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Estrogen Therapy In Atropic Vaginitis

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OURS IS AN aging population and the trend is especially pronounced among women. Even in this context, however, the familiar term *senile vaginitis* leaves something to be desired; it is neither as broad nor as specific as *atrophic vaginitis*. The latter term encompasses not only age-associated manifestations, but also those relating to surgical or radiologic castration. At the same time it literally designates the essential pathologic state—atrophy of the vaginal epithelium (sometimes extending to subepithelial structures) with consequent dysfunction. Whether the surrounding circumstances are chronologic or iatrogenic, the underlying common factor is a reduction in available endogenous estrogen. This may occur during the early climacteric years after the menopause, or in younger women with severe ovarian deficiency.

The patient most frequently presents herself for gynecologic care because of vaginal burning, itching and dyspareunia. Pelvic examination reveals a thin watery discharge from a friable vaginal mucosa devoid of rugae. The latter appears thin, almost transparent, glistening and inflamed, and bleeds with minimal trauma. Not infrequently, areas of shallow ulceration are seen. Vaginal smears prepared for cytohormonal evaluation show numerous parabasal cells with a paucity of superficial cornified cells; i.e., poor maturation index.

In addition to the routine gross and cytologic examinations mentioned above,* the magnifying optical system of the colposcope makes possible stereoscopic visualization of the vulva, vagina and cervix at magnifications of ten to twenty times under direct illumination.[20] Color colpophotography can provide permanent objective data,

* *Colposcopy and colpophotography have proven a valuable diagnostic adjunct.*

PATIENT L.G.: 57 years old, menopause at age 50; PMH: negative; OB Hx: para 5, gravida 7, ab. 2; atrophic changes; ext. gen., vag., and cvx.; wet smear: neg. trich. and fungi; Pap smear: class I; Dx: postmenopausal atrophic vaginitis.

FIGURE 1A: ABOVE, LEFT—Patient L.G. before treatment.

Left to right: Color colpophotographs of vulva, vagina and cervix; note thinning and micropetechial hemorrhages of vaginal and cervical mocosa. Below, left: Vaginal cytology with numerous parabasal cells. Below, right: Histologic section from mid-posterior vaginal wall showing thin, atrophic epithelium.

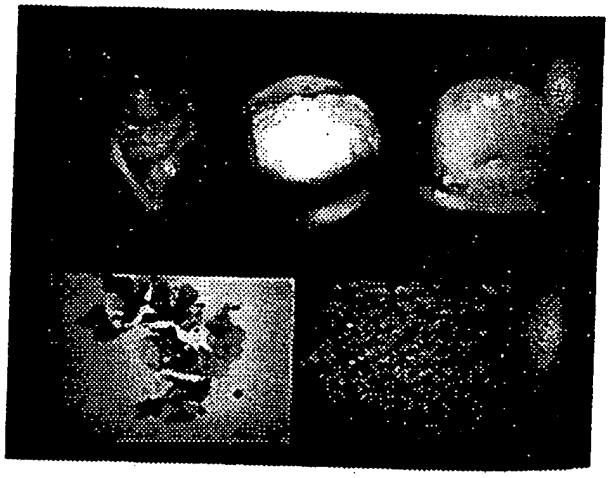

FIGURE 1B: ABOVE RIGHT—Patient L.G. after 4 weeks of treatment (intravaginal application of dienestrol cream). Left to right: Color colpophotographs of vulva, vagina and cervix show restoration of normal mucosal thickness and formation of vaginal rugae. Below, left: Vaginal smear evidencing good estrogenic effects. Below, right: Histologic section showing normal thickness of vaginal mucosa (mid-posterior wall) with superficial hyperkeratosis and acanthosis.

TABLE I. EVALUATION OF CLINICAL RESPONSE

	Excellent	Good	Fair	Poor	Total
Patients on suppository (group A)	21	6		1 (4%)	28
Patients on cream (group B)	9	4	2	1 (6%)	16

Excellent = Complete clinical relief of symptoms and lush vaginal mucosa typical of women of childbearing age.

Good = Complete clinical relief of symptoms and good appearance of mucosa (But not appearance as in young women).

Fair = Clinical improvement and improved appearance of mucosa (not the desired end-point).

Poor = Little or no change.

obtained from individual cases, to help discern and document the severity of involvement. Under colposcopic control, vaginal biopsies can be taken to add another diagnostic approach—and also a standard for the evaluation of therapy.

In the years since hormonal treatment has become available to the clinician, the presence of atrophic vaginitis suggests the possibility of some type of estrogen supplementation therapy. As one reviews the literature, the question of therapeutic approach—local versus oral or injectable[18]—still remains an unsettled issue.

Materials and Methods

In this study, estrogenic treatment in the form of dienestrol was applied locally (as intravaginal suppository or cream) in the treatment of a group of women with atrophic vaginitis. Forty-four patients are reported on; five others originally in the study are not analyzed as they were lost to follow-up.

Suppositories, each containing 0.7 mg. of dienestrol, were used by 28 patients (group A), while 16 women used a 0.01 per cent dienestrol cream (group B). One applicatorful of the latter delivers approximately the same dose of dienestrol as a single suppository. Each patient followed an identical course of treatment, consisting of a single intravaginal insertion of suppository or cream nightly for two weeks followed by an every-other-night regimen for two weeks.

The study group included 26 private out-patients (16 on cream, 10 on suppository) and 18 in-patients (all on the suppository) treated at a home for the aged. The patients ranged in age from 49 to 92 years; of these, 12 patients were under 60 years; 14 patients, 60 to 69 years; and 18 patients were 70 years and over. In the latter category, 16 patients were residents of the old-age home (where only suppositories were used).

Before starting treatment, all patients were examined; the physical clinical condition of the vulva, vagina and cervix was observed and recorded; cervicovaginal smears were taken for cytohormonal* and Papanicoloau** determinations. In addition, wet smears were reviewed to rule out trichomoniasis; candidiasis cultures*** were also taken and reviewed. A positive result on any of these tests excluded the patient from the study. Identical testing was repeated after the first two weeks of treatment; this provided a two-stage assessment of clinical response and cytologic status. In recording maturation indices, a slide rated unsatisfactory (superficial and intermediate cells absent) was assigned a nominal value of 1 per cent superficial cells, to permit statistical analysis of the data and the tabulation of geometric means.

In addition to the 44 statistically analyzed cases, another 4 patients with atrophic vaginitis—2 treated by intravaginal application of dienestrol suppositories—were studied not only by the clinical and laboratory procedures described, but also by colposcopic examinations of the vulva, vagina and cervix uteri. Observations were recorded by color colpophotography prior to treatment, after two weeks, and after four weeks of treatment. In all 4 of these patients, vaginal spot biopsies were taken from the mid-posterior vaginal wall, under colposcopic guidance, prior to and after four weeks of treatment. Colpophotographic, cytohormonal and histologic findings for one of these 4 patients, pre-treatment and post-treatment, are presented in Figures 1A and 1B.

* *A maturation index was performed and recorded primarily on the basis of superficial cells observed.*

** *Papanicoloau smear classifications: I for 41 patients; II for 2 patients; smear unsatisfactory for one patient.*

*** *Cultures on Nickerson's medium were checked for candida organisms.*

Results

Clincially (in terms of symptomatology and gross visualization) almost all patients responded with some degree of improvement to the dienestrol medication. The vaginal suppository (used in group A) apparently gave slightly better results than the cream (used in group B). Moreover, patients in the former group were older, and presented generally a greater severity

TABLE II. SUB-GROUP MATURATION INDICES

Geometric Means of Superficial Cell Percentages

	UNDER 60				60 TO 69			
	Start	2 wks.	4 wks.	No. Pts.	Start	2 wks.	4 wks.	No. Pts.
Suppos. (group A)	15.3	76.3	56.7	(4)	17.6	74.9	59.6	(7)
Cream (group B)	31.6	67.8	66.0	(8)	14.7	56.7	59.9	(7)
All Pts.	24.8	70.6	62.8	(12)	16.1	65.2	59.7	(14)

	70 AND OVER				ALL AGES			
	Start	2 wks.	4 wks.	No. Pts.	Start	2 wks.	4 wks.	No. Pts.
Suppos. (group A)	18.5	61.7	54.7	(17)	17.8	66.8	56.1	(28)
Cream (group B)	37.0	44.0	1.0	(1)	22.9	61.0	48.7	(16)
All Pts.	19.3	60.5	43.8	(18)	19.5	64.6	53.3	(44)

of involvement prior to treatment.

Cytologically, the over-all results of treatment (age-corrected) as shown in Table 2, reveal somewhat greater increases of maturation index in response to the suppository than to the cream, but these differences were not statistically significant.

Cytologic findings at two weeks and at four weeks were analyzed for the 34 patients in the group who had been found, at the start of the study, to have a superficial cell count below 45 per cent. Ten such patients were treated with cream; three of these (30 per cent) never reached the 60 per cent level during the study, four (40 per cent) reached a level above 60 per cent at two weeks and retained that level at four weeks, two (20 per cent) reached above 60 per cent level at two weeks but fell below at four weeks, and one (10 per cent) did not reach 60 per cent at two weeks but did so at four weeks. The other 24 patients with an initial value below 45 per cent were treated with suppository; six of these (25 per cent) never reached the 60 per cent level during the study, seven (29 per cent) reached a level above 60 per cent at two weeks and retained that level at four weeks, eight (33 per cent) reached above 60 per cent level at two weeks but fell below at four weeks, and three (13 per cent) did not reach 60 per cent at two weeks but did so at four weeks.

There were no reported side-effects and no untoward reactions were noted. Both forms of medication seemed to be fully acceptable; however, one patient stated that she had difficulty in using the cream.

Discussion

Several considerations have prompted previous investigators to prefer the intravaginal route for estrogen treatment in atrophic vaginitis. These include patient acceptability and the avoidance of various side effects sometimes ascribed to estrogen given orally or parenterally.[1,4,17,19] As regards the latter, it has been pointed out that systemic estrogens are rarely, if ever, indicated in patients with localized pathology, because of possible undesirable effects on the endometrium[4,5] and a tendency to produce breast tenderness and breast cysts.[18] On the other hand, the relative safety of intravaginal estrogen therapy (even over prolonged periods of use)[1,2] recommended this route as a logical way to restore the vaginal epithelium to its former physiologic state.[3] In addition, Rakoff[17] has reported that, in instances of atrophic vaginitis, local therapy produces a more rapid effect. Over the course of several weeks, in the experience of most investigators, a thick, velvety mucosa is usually produced, with good cornification of the superficial epithelium.[10,11,20] In specific instances, antibacterial agents combined with estrogen have also been used with success.[6,9] Falk and Hassid,[12] prior to vaginal plastic procedures, treat all patients of peri-menopausal age with estrogen cream applied vaginally, in an effort to render the the vaginal mucosa less friable at the time of operation. They recommend postoperative continuation of this form of therapy to assist in re-epithelization of the vagina.

In our group of study patients, the therapeutic effectiveness of intravaginal dienestrol, in both cream and suppository form, was highly satisfactory, as judged by clinical, colposcopic, vaginal (biopsy) and cytologic improvement. Cytohormonal indices reflect improvement as regards epithelial proliferation and maturation. It is possible, however, in view of the "falling below" seen at four weeks in those patients with a starting count value below 45 per cent, that a more successful cytologic response might have been elicited by extending the higher-frequency (nightly) dosage regimen, and perhaps also by preferential use of the suppository form, which seemed to confer some advantage.

Colposcopic examinations of the vulva, vagina and cervix during and after the treatment, as well as vaginal punch biopsies from the mid-posterior vaginal wall, proved to be useful aids in the diagnosis and treatment of atrophic vaginitis. Although estrogen administration in the menopause has proponents as well as opponents[13], the experience of this study gives further support to the validity of the basic concept that treatment of atrophic vaginitis with the topical medications employed can be effective, simple, and devoid of systemic problems.

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Summary

The intravaginal application of dienestrol (cream and suppositories) in 48 cases of atrophic vaginitis was found to be an effective and acceptable method of treatment; the quantity of hormone required by local application is relatively small and therapeutic effect can be obtained rapidly and without the induction of systemic symptoms.

Acknowledgment

DV (dienestrol) Suppositories and DV (dienestrol) Cream were made available for clinical investigation by the producer of these medications, The National Drug Company, Division of Richardson-Merrell Inc., Philadelphia, Pennsylvania. Trademark: DV □

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ORIGINAL ARTICLE

Comparison of usefulness of estradiol vaginal tablets and estriol vagitories for treatment of vaginal atrophy

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Acta Obstet Gynecol Scand 2000; 79: 293–297. © Acta Obstet Gynecol Scand 2000

Background. Atrophic vaginitis is a common condition. This study compared the usefulness of estradiol vaginal tablets (EVT) and estriol vagitories (EV) in treatment of atrophic vaginitis.
Methods. Ninety-six postmenopausal women with symptoms of atrophic vaginitis were treated for 24 weeks with either EVT or with EV. Patients used the medication daily for the first 2 weeks of the study, and twice-weekly thereafter.
Results. Both EVT and EV were effective in treating vaginal atrophy and patients in both treatment groups experienced a significant improvement in vaginal symptoms such as itching, irritation, dryness, and dyspareunia. At the end of the study three (6%) EVT treated women reported leakage and none needed to use sanitary towels. Among the EV treated women 31 (65%) reported leakage and 14 (29%) required sanitary protection. Furthermore, 90% in the EVT group perceived the medication as hygienic compared to 79% in the EV group, and 49% in the EVT group indicated that the product was easy to use compared to 28% in the EV group. Endometrial thickness was increased (1.1 mm with EVT and 0.5 mm on EV) in both treatment groups during the first 2 weeks of the study, but returned to baseline levels when the frequency of drug application was reduced to twice-weekly.
Conclusions. Estradiol vaginal tablets provides an effective alternative to traditional forms of local estrogen therapy.

Key words: atrophic vaginitis; estradiol vaginal tablet; Vagifem; estriol vagitory; Ovesterin; patient acceptability; postmenopausal women

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The decline in circulating estrogen levels after the menopause has deleterious effects on the urogenital system, with up to 50% of postmenopausal women experiencing some degree of discomfort (1, 2). Symptoms of vaginal atrophy typically do not become apparent until some time after the menopause once acute climacteric symptoms, such as menstrual irregularities, hot flushes, fatigue, and depression, have abated. This has implications for clinical management since, because symptoms are localized, systemic hormone replacement therapy (HRT) may not be required. This is important as older women are often reluctant to use systemic HRT (3, 4).

Vaginal application of estrogen is known to be effective in the treatment of atrophic vaginitis (5). Until recently, estriol vagitories and vaginal creams have been the most common forms of local estrogen therapy in Europe. They are often considered to be unhygienic by patients and both forms are associated with leakage from the vagina, often necessitating the use of some form of sani-

Abbreviations:
EVT: estradiol vaginal tablets; EV: estriol vagitories: HRT: hormone replacement therapy; FSH: follicle stimulating hormone.

tary protection. These factors have impact on patient acceptability and compliance with therapy (6). This is of clinical significance since symptoms of atrophic vaginitis often require long-term treatment (7). Vagifem® (Novo Nordisk A/S) is a low-dose, slow-release vaginal tablet containing 25 μg 17 β-estradiol. The tablet is small (6 mm in diameter) and is placed deep into the vagina with a disposable applicator. It adheres to the vaginal mucosa in a controlled manner with minimal discharge (6). The present study compared the acceptability, efficacy and safety of the estradiol vaginal tablet with that of estriol vagitory.

Subjects and methods

Subjects

Postmenopausal women aged 50–70 years with signs and symptoms of vaginal atrophy and who did not require systemic estrogen therapy for the treatment of vasomotor symptoms or prophylaxis of osteoporosis and had not experienced vaginal bleeding for at least 1 year were eligible to participate in this study. Participants were not permitted to have taken systemic or vaginal estrogen therapy within the 6 months prior to the study. Women were also excluded if they had any history of carcinoma of the breast or endometrium, abnormal genital bleeding, acute thrombophlebitis, or thromboembolic disorders associated with previous estrogen use, or current urinary or vaginal infection.

Study design

This was a randomized, parallel-group, single-blind, multicenter trial. Women were randomized to receive either estradiol vaginal tablets (25 μg 17 β-estradiol) or estriol vagitories (0.5 mg estriol). The study medication was administered once-daily for the first 2 weeks of the study (labeling for Ovesterin in Norway states once-daily for 3 weeks) and twice-weekly thereafter. The total duration of treatment was 24 weeks. Given the different methods of study drug application, an independent person was assigned to dispense the medication to maintain blinding of the study investigator. The study was approved by local ethics committees and conducted in accordance with the Declaration of Helsinki (Hong Kong revision, 1989). All participants gave written, informed consent.

Acceptability

The formulations were applied by the patient. Patient acceptability of the study medication (presence and degree of pain during application, leakage of medication and subsequent need to use sanitary towels, as well as overall hygienic value and general user-friendliness) were assessed after 2 weeks of treatment and at the end of the trial using a patient questionnaire. Leakage of medication after application was similarly evaluated by 'yes/no' boxes, with 'yes' answers requiring a further 'yes/no' answer for the need to use sanitary towels. Hygienic value was also evaluated by 'yes/no' boxes, while user-friendliness was evaluated using a three-point scale (very easy, easy, or difficult).

Efficacy and safety assessments

The degree of vaginal atrophy was assessed by the investigator at clinic visits at baseline and after 2, 12, and 24 weeks of treatment and graded on a four-point scale (non-atrophic, mild, moderate, or severe atrophy). In addition, a vaginal maturation was derived from vaginal smears taken on entry into the trial and at weeks 2 and 24. To ensure standardization of results, all slides were evaluated by a single cytopathologist who was blinded to the study medication.

At each clinic visit, the severity of atrophic vaginitis symptoms (vaginal dryness, irritation, itching, dyspareunia, libido, and dysuria) were graded by the patients using a visual analog scale (VAS; range 'none' to 'extreme' for each symptom). Women were also asked whether they had experienced vaginal bleeding, recurrent vaginal discharge, or stress or urge incontinence. The women provided a global evaluation of the effect of menopausal symptoms at baseline (not bothered, slightly bothered, or very bothered) and change after 2, 12, and 24 weeks of treatment (much better, better, unchanged, worse, or much worse). Diary cards were used to record the severity of vaginal symptoms of sensitivity, itching, dryness, and dysuria, as well as global symptom severity and improvement. Women were instructed to fill out the diary cards on a daily basis for the first 2 weeks of the study, and on a weekly basis thereafter.

Serum follicle-stimulating hormone (FSH) and estradiol levels were evaluated at study baseline and after 24 weeks of treatment. Endometrial thickness was measured at the time of entry into the trial and after 2, 12, and 24 weeks of therapy using transvaginal ultrasound -5.0 to 7.5 MHz transvaginal probe. After identifying the mid-sagittal plane, the thickest anteroposterior diameter of both layers of the endometrium are measured with an electronic calipers.

Any adverse events were also recorded at these times.

Statistical analysis

An intent-to-treat analysis was performed. Data were tested for difference between treatment groups using the Student test for continuous data and the Chi-square or Fisher Exact test for categorical data. All analysis were two-tailed and performed to a significance level of 95%.

Sample size calculation

The primary variable used in the sample size calculation was the patients rating of symptom severity on a 10 cm Visual Analog Scale. The variable was assumed to be continuously distributed with equal dispersion within the two treatment groups. Both the Type I and Type II errors were set to 5%. By using an ANOVA model with a logarithmic correction for centers, a total of 46 patients had to be included in each group (8).

Results

Demography

A total of 96 women entered the trial, 48 in each treatment group. The two treatment groups were well matched for patient characteristics at baseline (Table I). Sixteen (33%) women randomized to EVT and nine (12.5%) of those who received EV had previously taken some HRT; however, intergroup differences were not statistically significant (p=0.10).

Eleven patients withdrew from the study (six of those receiving EVT and five on EV). Of the patients receiving EVT, three withdrew due to adverse events – paresthesia, leucorrhea, endometrial disorder (no malignancy) – two due to non-compliance, and one due to medical problems – hypothyroidism. On those receiving EV, two patients withdrew from the study because the treatment was ineffective, two because they did not attend clinic visits, and one patient due to personal problems.

Table I. Patient characteristics at study baseline (mean s.d.)

	Estradiol vaginal tablet (n=48)	Estriol vagitories (n=48)
Age (years)	58.2 (4.9)	59.3 (5.3)
Height (cm)	165.5 (5.5)	163.6 (4.6)
Weight (kg)	68.8 (10.6)	65.8 (10.1)
Age at menopause (years)	49.2 (4.0)	49.9 (3.5)
Prior HRT use (n)	16	9

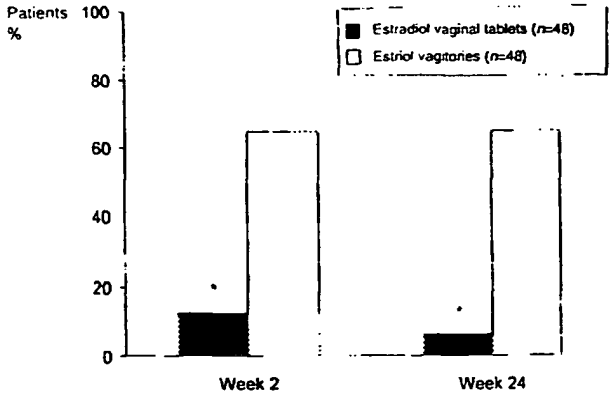

Fig. 1. Percentage of women reporting leakage of medication from the vagina after 2 and 24 weeks of treatment with estradiol vaginal tablet of estriol vagitories. * $p \leq 0.0001$ *vs* estriol vagitories.

Acceptability

In contrast to the EVT treatment group, most women receiving EV experienced discharge of medication following application throughout the 24-week treatment period (Fig. 1). After 2 weeks of treatment, only six (12%) of the EVT-treated women reported leakage of medication from the vagina compared with 31 (65%) of those who had received EV. The difference between treatment groups was highly significant (p=0.0001) and had increased by the end of the study, when only three (6%) women in the EVT-treatment group reported leakage compared with 31 (65%) in the EV group (p=0.0001).

The need to use sanitary towels was found to be correspondingly higher in the EV treatment group throughout the trial. After 2 weeks of treatment, medication leakage necessitated the use of sanitary towels by only three (6%) of the women receiving EVT compared with 22 (46%) of those in the EV treatment group. Following the reduction of study drug administration to twice-weekly, none of the women treated with EVT required sanitary towels while 14 (14%) of those receiving EV still needed to use them.

The above findings also correspond to the hygienic value and user-friendliness of the two study medications. After 2 weeks of treatment, all of the women in the EVT treatment group considered the product to be hygienic compared with 41 (85%) of those who received EV (p=0.01). A trend in favor of EVT for hygiene was still apparent at the end of the treatment period (90% versus 79%, respectively; p=0.06). Similarly, at the end of the trial, more of the women in the EVT treatment group than in the EV group indicated that the product was very easy to use (49% versus 28%, respectively).

		Maturation			Atrophy				
Group	N	H	M	L	L	M	H	DF	ND
EVT									
0 W	37	9	4	11	7	3	3	11	0
2 W	43	29	7	4	0	1	2	4	1
24 W	39	23	10	5	0	0	1	5	4
EV									
0 W	36	5	8	13	0	6	6	11	1
2 W	47	32	8	8	0	0	1	1	0
24 W	40	20	10	9	0	1	0	3	5

Fig. 2. Cytology results. Where: N=number with acceptable smear; L=low high level of maturation or atrophy; M=medium level of maturation or atrophy; H=high level of maturation or atrophy; DF=number with diagnosis failure or unacceptable smear; ND=number without a smear taken; W=week.

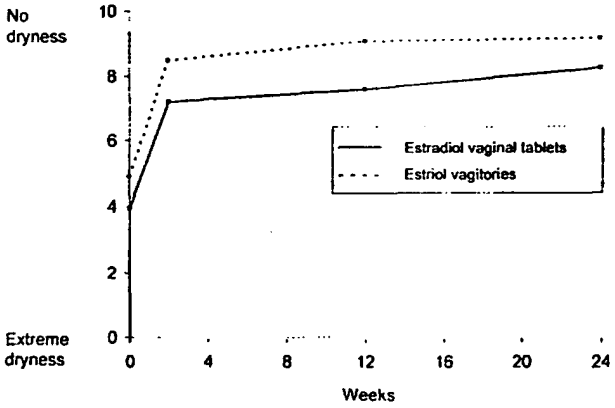

Fig. 3. Mean patient rating of dryness on a 10 cm visual analog scale.

Efficacy

Investigator assessments revealed that the level of vaginal atrophy improved in both treatment groups over the 24-week treatment period, with no significant differences detected between the two therapies. The cytology results support this finding (Fig. 2). Analysis of the vaginal maturation revealed a rapid response to therapy in both treatment groups, such that by week 2 most smears had a majority of mature cells and very few were atrophic. This improvement was sustained throughout the treatment period.

Symptoms of vaginal itching, irritation, dryness, and dyspareunia improved significantly in both treatment groups over the course of the trial (p= 0.03 for itching and p=0.0001 for other symptoms). There were no significant differences between the two treatments, with the exception of vaginal dryness (p=0.0001 in favor of EV; Fig. 3.) No significant improvement was observed over time for the symptoms of libido and dysuria in either treatment group.

These findings are supported by the diary data as well as the patients' global evaluations of symptom severity and response to therapy. At study baseline most patients (75%) reported experiencing some distress as a consequence of their menopausal symptoms. By the second week of treatment, 21 (44%) EVT- and 26 (54%) EV-treated patients considered their status to be better or much better than previously. At completion of the study, 19 (40%) women in the EVT group reported further improvement, compared with 15 (31%) women in the EV group.

There was a transient increase in the number of women reporting vaginal discharge in both treatment groups after 2 weeks of therapy (12 and 8 in the EVT and EV groups, respectively). However, the number of women reporting vaginal discharge had returned to baseline levels (two per group) by week 12.

At the start of the study, incontinence was reported by 10 (21%) women in the EVT treatment group and 15 (31%) in the EV treatment group. At week 24 four patients (8%) in each treatment group were still experiencing incontinence.

Safety and tolerance

A total of 57 adverse events were reported during the study (27 on EVT and 30 with EV) (Table II). Of these adverse events, only four were considered to be related to treatment with EVT and six to EV. Blood estradiol levels were within the normal range for postmenopausal women (<0.01 nmol/l) after 24 weeks of treatment and serum FSH did not change. Endometrial thickness increased during the first 2 weeks of treatment in both treatment groups (1.1 mm with EVT and 0.5 mm on EV), but returned to baseline values by the end of the trial. There were no significant differences between treatment groups.

Discussion

Patient acceptability and preference is an important aspect of local estrogen therapy. The treatment should be easy and convenient, since long-term

Table II. Adverse events considered possibly or probably related to therapy

Adverse event	Estradiol vaginal tablet (n=48)	Estriol vagitories (n=48)
Vaginal itching	2	1
Vaginal discomfort	0	1
Breast pain	1	0
Abdominal pain	0	1
Paresthesia	1	1
Nausea	0	1
Insomnia	0	1
Total	4	6

therapy is likely to be necessary (7). Despite the well-documented efficacy of treatment with estriol vagitories, compliance with therapy can be poor (9, 10). A major reason for this is likely to be the leakage of medication from the vagina, which usually necessitates the use of sanitary protection (6).

The present study confirms that leakage of medication is significantly less common with EVT than with an estriol vagitory. The better patient acceptability of vaginal tablets compared with vaginal suppository is likely to improve compliance of long-term therapy with vaginal tablets. This is supported by a recent study demonstrating that women treated with EVT were more likely to remain on therapy than those who were treated with a vaginal cream (11).

Estradiol vaginal tablets were found to be an effective alternative to traditional local estrogen therapy for the treatment of atrophic vaginitis in postmenopausal women. This is consistent with the results of previous clinical trials with treatment durations of up to 2 years (5, 11–16).

No statistical analysis could be performed on cytology due to the small numbers in each index. Although the karypyknotic index is the relevant and objective parameter, it is the subjective symptoms as evaluated by the clinician which are treated.

Blood estradiol levels did not rise and FSH levels did not fall. Although endometrial thickness slightly increase in the first two weeks of daily treatment with both study medications, this effect vanished during the course of trial. These findings, consistent with the results of other studies (12, 15, 16), show that systemic absorption of estrogen during twice-weekly treatment with EVT is negligible and unlikely to be of clinical significance.

In conclusion, the estradiol vaginal tablet is as effective as estriol vagitory. In treatment of atrophic vaginitis estradiol vaginal tablets produced, however, significantly less vaginal leakage and requirement for sanitary protection.

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17β-Estradiol Vaginal Tablet Versus Conjugated Equine Estrogen Vaginal Cream to Relieve Menopausal Atrophic Vaginitis

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ABSTRACT

Objectives: The efficacy and safety of 25-μg 17β-estradiol vaginal tablets (Vagifem) were assessed and compared with 1.25-mg conjugated equine estrogen vaginal cream (Premarin Vaginal Cream) for the relief of menopausal-derived atrophic vaginitis, resulting from estrogen deficiency.

Design: In a multicenter, open-label, randomized, parallel-group study, 159 menopausal women were treated for 24 weeks with either vaginal tablets or vaginal cream. Efficacy was evaluated by relief of vaginal symptoms and concentrations of serum estradiol and follicle-stimulating hormone. Safety was monitored by the incidence of adverse events, evaluation of endometrial biopsies, and clinical laboratory results. Patients also assessed the acceptability of the study medications.

Results: Composite scores of vaginal symptoms (dryness, soreness, and irritation) demonstrated that both treatments provided equivalent relief of the symptoms of atrophic vaginitis. At weeks 2, 12, and 24, increases in serum estradiol concentrations and suppression of follicle-stimulating hormone were observed in significantly more patients who were using the vaginal cream than in those who were using the vaginal tablets ($p < 0.001$). Fewer patients who were using the vaginal tablets experienced endometrial proliferation or hyperplasia compared with patients who were using the vaginal cream. Significantly more patients who were using the vaginal tablets rated their medication favorably than did patients who were using the vaginal cream ($p \leq 0.001$). Patients who were receiving the vaginal tablets also had a lower incidence of patient withdrawal (10% versus 32%).

Conclusions: Treatment regimens with 25-μg 17β-estradiol vaginal tablets and with 1.25-mg conjugated equine estrogen vaginal cream were equivalent in relieving symptoms of atrophic vaginitis. The vaginal tablets demonstrated a localized effect without appreciable systemic estradiol increases or estrogenic side effects. Vaginal tablet therapy resulted in greater patient acceptance and lower withdrawal rates compared with vaginal cream therapy. (*Menopause* 2000;7:156–161. © 2000, The North American Menopause Society.)

Key Words: Estrogen replacement therapy – Menopause – Vaginal atrophy – Vaginal cream – Vaginal tablets.

Estrogen-dependent tissues, such as the vaginal epithelium, begin to undergo atrophic changes when endogenous estrogen concentration declines during menopause. Atrophic vaginitis is a common and often untreated condition of urogenital aging in postmenopausal women.[1] The principal symptoms of urogenital aging are a thin, friable vaginal mucosa; vaginal dryness; irritation; and sexual discomfort. Atrophic vaginitis can compromise a woman's quality of life and bring about sexual problems that result from painful intercourse, micturition, and incontinence.[2] However, few women receive therapy for these symptoms because of a combination of patient embarrassment, underdiagnosis, and the greater attention given to preventing and treating the more prominent gynecogeriatric concerns of

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cardiovascular, osteodegenerative, neoplastic, and degenerative diseases.[3]

Until recently, only a small percentage of women who experienced atrophic vaginitis received estrogen treatment.[1] The use of orally administered and locally applied estrogen replacement therapies (ERTs), including conjugated equine estrogen vaginal cream (Premarin Vaginal Cream; Wyeth-Ayerst, Philadelphia, PA, USA), has become more widespread but can result in increased systemic estradiol (E2) concentrations.[4] An ideal treatment to relieve the vaginal symptoms of estrogen deficiency would have a localized effect, without a concurrent increase in serum E2, and would be safe, convenient, and easy to apply.[5] A low-dose (25 μg) 17β-estradiol vaginal tablet (Vagifem; Novo Nordisk A/S, Copenhagen, Denmark) has been developed to treat atrophic vaginitis resulting from menopausal estrogen deficiency.

This study evaluated and compared the safety and efficacy of 25-μg 17β-estradiol vaginal tablets and 1.25-mg conjugated equine estrogen vaginal cream during 6 months of therapy for vaginal atrophy.

MATERIALS AND METHODS

This was a prospective, multicenter, open-label, randomized, parallel-group study conducted at six centers in Canada. The study was approved by the appropriate institutional review boards, and informed consent was obtained from each patient.

A total of 159 women, aged 42–85 years (mean age = approximately 57 years), with intact uteri and two or more vaginal symptoms (dryness, soreness, or irritation) rated as moderate to severe, were enrolled. Patients were required to be at least 1 year past menopause and have serum E2 concentrations of 30 pg/mL (110 pmol/L) or less and follicle-stimulating hormone (FSH) concentrations of 40 IU/L or more. Women who had a known or suspected history of breast carcinoma, estrogen-dependent neoplasia, positive or suspicious mammogram results, or any systemic malignant disease were excluded from the study, as were women who had abnormal vaginal bleeding, uterine bleeding of unknown cause, or a history of thrombolytic disorders. During the 3 months before the study, women were not to have received hormone therapy (i.e., sex hormones, steroids, or vaginal treatments).

Patients were randomized using a predetermined, computer-generated scheme. Eighty patients were treated with 17β-estradiol vaginal tablets, and 79 patients were treated with conjugated equine estrogen vaginal cream. Patients in the vaginal tablet treatment group inserted one tablet intravaginally once daily for 2 weeks. Thereafter, patients inserted one tablet twice per week with at least a 3-day interval between treatments to maintain therapeutic response. Patients in the vaginal cream treatment group applied 2 g vaginal cream (equivalent to 1.25 mg conjugated equine estrogens) daily for 21 days, withheld treatment for 7 days, and then repeated the regimen. In this study, the vaginal cream was used according to the dose and regimen recommended by both U.S. and Canadian labeling at the time the study was conducted. The efficacy of vaginal cream for the treatment of atrophic vaginitis has been established previously.[6,7] Patients were evaluated for efficacy and safety at week −4 (screening) and at weeks 0, 2, 12, and 24. Patients were also contacted by telephone between weeks 5 and 6 and between weeks 17 and 19.

Efficacy assessments for each treatment were based on relief of the atrophic vaginitis symptoms of dryness, soreness, and irritation. Patients evaluated these symptoms using intensity ratings of none, mild, moderate, or severe. Vaginal appearance was assessed by the investigator during gynecological examination using the same intensity scale. Efficacy evaluations also included serum concentrations of E2 and FSH, which were measured by radioimmunoassay and chemiluminescence, respectively, to determine possible systemic absorption of E2 resulting from the treatments.

Intensity ratings for each of the vaginal symptoms (dryness, soreness, and irritation) were assigned ascending scores from 0 (none) to 3 (severe) for analysis. To avoid multiple endpoint issues, a composite score was defined as the average of the individual symptom scores. A test of linear association between symptoms was performed within each treatment group using data for the change from baseline in individual symptom scores at week 12. The Pearson correlation coefficients between each pair of symptoms ranged between 0.186 and 0.664. Although the magnitude of the correlation was not strong because of the nature of categorical data, each pair of symptoms was positively linearly associated (significantly or borderline significantly; $p \leq 0.101$ using the Mantel-Haenszel χ^2 test). Therefore, the composite score provided a reasonable overall evaluation of the treatment effect in relieving the vaginal symptoms.

Changes from baseline in the vaginal symptom composite scores were analyzed and compared using an analysis of variance model that accounted for center and treatment. Two-sided 95% confidence intervals were calculated for the observed means, and the estimated variance was derived from the analysis of variance model. Assuming equivalent efficacy between the two treatments, the sample sizes of the enrolled populations yielded a 90% chance that the observed mean

differences in efficacy variables would lie within the 95% confidence interval.

Safety assessments were based on the occurrence of adverse events (AEs); vital signs; and the results of endometrial biopsies, Pap smears, and clinical laboratory tests. AEs and vital signs were recorded at each visit. Endometrial biopsies and Pap smears were performed at the screening visit (week −4) and at the final visit (week 24). Blood samples were drawn by venipuncture at the screening visit; at weeks 2, 4, and 12 during the treatment period; and at the final visit (week 24) for routine chemistry, hematology, and hormone evaluations.

Endometrial biopsies were evaluated by two independent pathologists who were blinded to treatment and to the other's interpretation. Differing interpretations were adjudicated by a third pathologist who was similarly blinded. If all three interpretations were different, the third pathologist conducted another reading.

Throughout the study, patients also rated their medication in terms of ease of administration (difficult, acceptable, or easy), comfort of administration (uncomfortable, acceptable, or comfortable), and overall acceptability (unacceptable, acceptable, or very acceptable).

RESULTS

One hundred fifty-nine women were treated: 80 with vaginal tablets and 79 with vaginal cream. Their baseline characteristics are listed in Table 1. In the vaginal tablet treatment group, 72 patients (90%) completed the study and 8 patients (10%) discontinued prematurely (4 because of AEs, 2 because of noncompliance with the protocol, and 1 each because of withdrawal of consent and an E2 level that did not meet eligibility criteria). In the vaginal cream treatment group, 54 patients (68%) completed the study and 25 patients (32%) discontinued prematurely (14 because of AEs, 8 because of noncompliance with the protocol, 2 because of messy or cumbersome application of the cream, and 1 because of an E2 level that did not meet eligibility criteria). As shown in Figure 1, a higher percentage of patients in the vaginal tablet treatment group than in the vaginal cream treatment group continued in the study at each week of treatment. During the first 2 weeks of the treatment period, a larger number of patients discontinued treatment with the vaginal cream compared with the vaginal tablets. The reasons given at the time of discontinuation included primarily AEs and a subjective dislike of the cream.

Treatment with both vaginal tablets and vaginal cream provided quick and sustained relief of vaginal symptoms, as indicated by decreases in the vaginal symptom composite score (Fig. 2). Composite scores for both treatment groups were comparable and showed

TABLE 1. *Baseline and demographic characteristics*

	Vaginal tablets (n = 80)	Vaginal cream (n = 79)
Age (y)[a]	57.3 ± 7.1	57.2 ± 7.8
Height (cm)[a]	161.5 ± 4.8	162.5 ± 5.9
Weight (kg)[a]	64.4 ± 9.0	69.3 ± 13.4
Time since last menses (y)[a]	7.9 ± 7.0	7.6 ± 7.2
Prior treatment with HRT, n (%)		
Yes	26 (33)	32 (41)
No	54 (68)	47 (59)
Prior treatment for atrophic vaginitis, n (%)		
Yes	14 (18)	12 (15)
No	66 (83)	67 (85)

HRT, hormone replacement therapy.
[a]Mean ± SD.

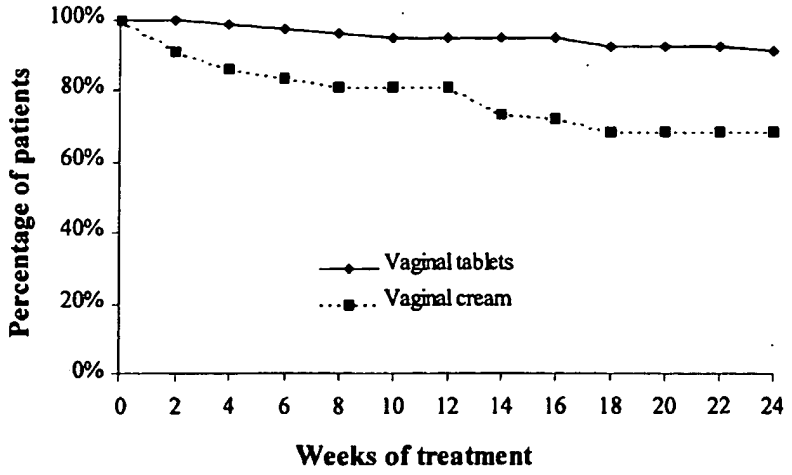

FIG. 1. Percentage of patients continuing in the study.

improvement during the course of the study. This improvement was also observed in the individual symptom and atrophy scores (Table 2). At week 24, patients in both treatment groups experienced substantial improvement from baseline in their assessments of vaginal dryness, soreness, and irritation. At the same time point, vaginal atrophy (vaginal appearance score), as assessed by the investigator, was also improved from baseline.

At each time point, patients in the vaginal tablet group had significantly fewer instances of increased E2 levels above the normal postmenopausal range (>49 pg/mL) than those in the vaginal cream group ($p < 0.001$) (Fig. 3). This difference between treatment groups was expected as a result of the vaginal cream dosing regimen. At week 24, 3 patients (5%) in the vaginal tablet group and 21 patients (47%) in the vaginal cream group experienced increased E2 levels. Of these patients, 1 patient (33%) in the vaginal tablet group and 10 patients (48%) in the vaginal cream group also had a concomitant decrease in FSH levels below the normal postmenopausal range (≤35 IU/L).

The most frequently reported AEs involved the reproductive system. Uterine bleeding, breast pain, and perineal pain were reported by 9% of patients who were using the vaginal tablets and by 34% of patients who were using the vaginal cream. One patient discontinued use of the vaginal tablets because of postmenopausal bleeding. No other patients discontinued use of the vaginal tablets because of gynecologically related AEs. Six patients discontinued use of the vaginal cream because of gynecologically related AEs of perineal pain, genital pruritus, vaginitis, urinary tract infection, postmenopausal bleeding, and dysfunctional uterine bleeding.

Mean blood chemistry and hematology values for both treatment groups were within reference ranges at screening and at the end of treatment. Vital signs and physical and gynecological examination findings were characterized as normal both at screening and at the end

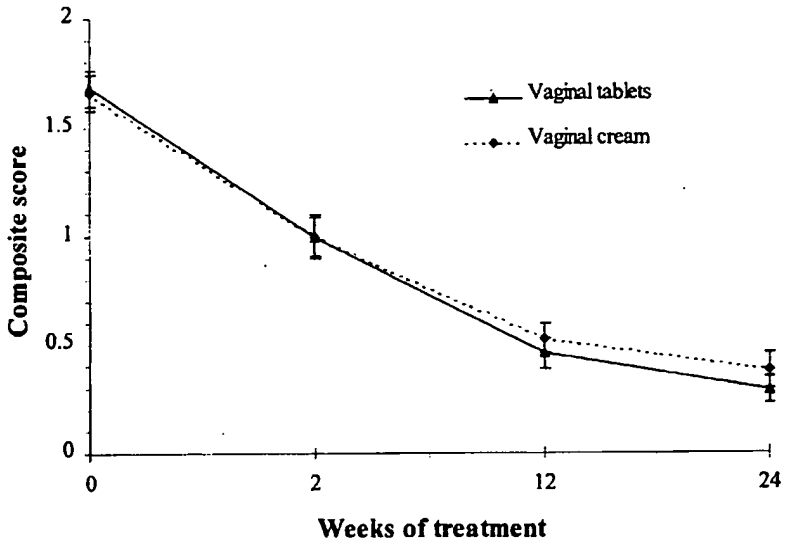

FIG. 2. Composite scores (mean ± SD) for vaginal symptoms. 0 = none; 1 = mild, 2 = moderate, 3 = severe.

TABLE 2. *Vaginal appearance and symptoms*

Treatment	Vaginal atrophy		Vaginal symptoms			
	n	[mean[a] (SD)]	*n*	Dryness [mean[a] (SD)]	Soreness [mean[a] (SD)]	Irritation [mean[a] (SD)]
Vaginal tablets						
Baseline[b]	78	2.6 (0.6)	79	2.2 (0.8)	1.4 (1.1)	1.4 (1.1)
Week 24	73	0.6 (0.7)	74	0.4 (0.7)	0.2 (0.5)	0.3 (0.6)
Vaginal cream						
Baseline[b]	72	2.6 (0.5)	71	2.1 (0.7)	1.5 (1.0)	1.4 (1.1)
Week 24	55	0.6 (0.8)	56	0.4 (0.7)	0.3 (0.6)	0.4 (0.7)

[a]Scores are reported on the following intensity scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe.
[b]Baseline for the vaginal atrophy assessment was defined as the screening visit, week −4. Baseline for the vaginal symptoms assessments was defined as the beginning of the treatment period, week 0. The number of patients at baseline reflects those who were treated, had baseline assessments for vaginal atrophy or symptoms, and returned for at least one postbaseline observation.

of the study. No patients required medical treatment during the study.

Endometrial biopsies were to be obtained at the screening visit and at the end of treatment (Table 3). At both time points, however, a number of patients did not undergo the biopsy procedure, which possibly can be attributed to the increased level of discomfort for patients who had atrophic vaginitis. At the end of the study (week 24), all patients in the vaginal tablet treatment group whose biopsies yielded sufficient tissue showed an atrophic endometrium, with the exception of one patient, who had a proliferative endometrium. In the vaginal cream treatment group, two patients had endometrial hyperplasia (one simple and one complex without atypia), seven patients had a proliferative endometrium, and four patients had a weakly proliferative endometrium.

At the end of the study, patients who had received the vaginal tablets rated the ease and comfort of administration and the overall acceptability of their medication more favorably than did patients who had received the vaginal cream (Fig. 4). Significantly more patients who had received the vaginal tablets reported ratings of easy, comfortable, and very acceptable in the respective categories compared with those who had received the vaginal cream ($p \leq 0.001$).

DISCUSSION

The 17β-estradiol vaginal tablets and the conjugated equine estrogen vaginal cream used in the present study are locally applied estrogen treatments that have been developed as alternatives/complements to conventional ERTs. After 2 weeks of daily therapy and 22 weeks of maintenance therapy, assessments by both investigators and patients indicated that the therapeutic effects of the vaginal tablets were comparable to those of the vaginal cream. Although the women who were treated with the vaginal tablets received a lower dose of estrogen than women who used the vaginal cream, both treatments were comparable in relieving the symptoms of atrophic vaginitis.

Endometrial hyperplasia is a known side effect of orally administered, unopposed estrogen treatments.[8–10] Locally applied estrogen therapies, such as the vaginal tablets and vaginal cream used in this study, were designed to treat vaginitis while minimizing the systemic absorption of E2 and the associated risk of endometrial hyperplasia. Substantially fewer patients who were treated with the vaginal tablets had E2 levels outside the normal postmenopausal range compared with patients who were treated with the vaginal cream. The smaller estrogen dose in the vaginal tablets compared with the vaginal cream

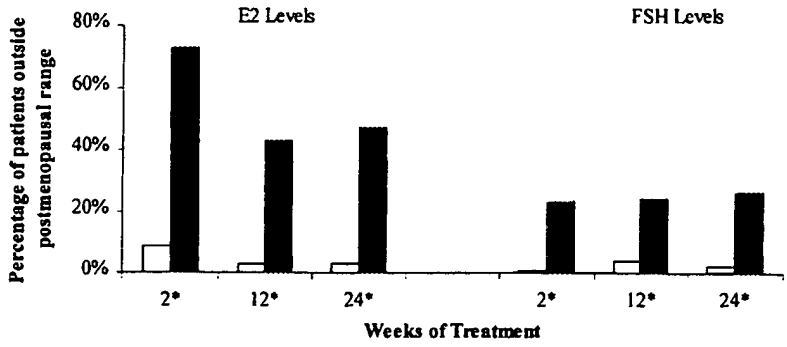

FIG. 3. Frequency of patients with estradiol (E2) and follicle-stimulating hormone (FSH) concentrations outside the postmenopausal range (E2 > 49pg/mL and FSH ≤ 35 IU/L). □ = vaginal tablets; ■ = vaginal cream; * = $p < 0.001$ (Fisher's exact test).

TABLE 3. *Endometrial biopsy results*

	Vaginal tablets ($n = 80$)		Vaginal cream ($n = 79$)	
	Baseline[a]	Week 24	Baseline[a]	Week 24
Patients with biopsies	60	49	59	49
Patients with stained biopsies				
Atrophic endometrium	34	34	35	15
Weakly proliferative endometrium	1	0	3	4
Proliferative endometrium	0	1	1	7
Endometrial hyperplasia	0	0	0	2
Biopsies with insufficient tissue	25	14	20	21

[a]Baseline for endometrial biopsy results was defined as the screening visit, week −4.

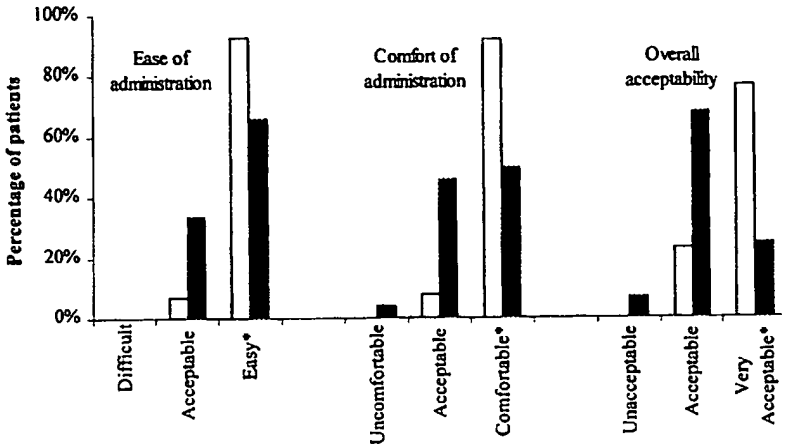

FIG. 4. Patient assessments of treatment at week 24. □ = vaginal tablets; ■ = vaginal cream; * $p \leq 0.001$ (Cochran-Mantel-Haenszel test).

(25 μg and 1.25 mg, respectively) likely contributed to this difference. The vaginal tablets also contain a hydrophilic, cellulose-derived matrix designed to provide a slow release of the low-dose E2, which also may have contributed to the minimal systemic absorption. The lower concentration of total systemic E2 achieved with administration of the vaginal tablets compared with that achieved with the vaginal cream was rarely associated with FSH suppression.

The increased absorption of E2 from the vaginal cream treatment group may also account for the increased incidence of endometrial abnormalities and E2-related side effects observed in these patients. In contrast, patients in the vaginal tablet treatment group had a lower incidence of AEs, and no patients experienced endometrial hyperplasia.

In this study, because a large percentage of patients did not undergo the biopsy procedure, the biopsy results may not be representative of all patients in the treatment groups. However, these results were similar to the results obtained for patients who received vaginal tablets in an independent 1-year study. During this 1-year study, the endometrial biopsies of 31 women who were receiving weekly administration of 25-μg 17β-estradiol vaginal tablets showed an atrophic endometrium for 29 women and a weakly proliferative endometrium for only 2 women.[11] In the same study, 9 women received twice-weekly administration of 25 μg 17β-estradiol intravaginally for 2 years, and all endometrial biopsies showed an atrophic endometrium.

Based on these results, 17β-estradiol vaginal tablets seem attractive as a single, local agent for the treatment of vaginal atrophy. Greater patient acceptance of the vaginal tablets over the vaginal cream could result in improved medication compliance and more consistent treatment of atrophic vaginitis.

Overall, both local treatments (17β-estradiol vaginal tablets and conjugated equine estrogen vaginal cream) proved to be comparably effective for the treatment of estrogen-derived atrophic vaginitis. The vaginal tablet offered the advantage of being well tolerated and having greater patient acceptability.

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Diagnosis and treatment of atrophic vaginitis

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Estrogen

Abstract:
Atrophic changes cause symptoms in the urogenital tract in almost one half of postmenopausal women. These changes result in vaginal symptoms such as vaginitis and dyspareunia and urinary symptoms, including urinary urgency, frequency and incontinence, as well as an increased frequency of urinary tract infection.

Full Text:

[Headnote]
Up to 40 percent of postmenopausal women have symptoms of atrophic vaginitis. Because the condition is attributable to estrogen deficiency it may occur in premenopausal women who take antiestrogenic medications or who have medical or surgical conditions that result in decreased levels of estrogen. The thinned endometrium and increased vaginal pH level induced by estrogen deficiency predispose the vagina and urinary tract to infection and mechanical weakness. The earliest symptoms are decreased vaginal lubrication, followed by other vaginal and urinary symptoms that may be exacerbated by superimposed infection. Once other causes of symptoms have been eliminated, treatment usually depends on estrogen replacement. Estrogen replacement therapy may be provided systemically or locally but the dosage and delivery method must be individualized. Vaginal moisturizers and lubricants, and participation in coitus may also be beneficial in the treatment of women with atrophic vaginitis. (Am Fam Physician 2000;61:3090-6.)

ecause of declining estrogen levels, women who are in mid-life or beyond often present with symptoms of atrophic vaginitis.

An estimated 10 to 40 percent of postmenopausal women have symptoms of atrophic vaginitis, also referred to as urogenital atrophy.1 Despite the prevalence of symptoms, only 20 to 25 percent of symptomatic women seek medical attention.2,3 Therefore, physicians have an opportunity to improve the urogenital health and quality of life of a large patient population through identification of and intervention in this often overlooked and underdiagnosed condition.

Throughout a woman's life cycle, the vaginal epithelium undergoes changes in response to the level of circulating estrogen. Stimulated by maternal estrogen, the vaginal epithelium is rugated and rich in glycogen in the newborn. During childhood, the epithelium remains thin until puberty, when it again thickens as a result of estrogen stimulation. Estrogen stimulation produces copious amounts of glycogen. Doderlein's lactobacilli depend on glycogen from sloughed vaginal cells.3 Lactic acid produced by these bacteria lowers vaginal pH levels to 3.5 to 4.5; this is essential for the body's natural defense against vaginal and urinary tract infections.4 Increased vaginal pH levels predispose the vagina to infection by streptococci, staphylococci, coliforms and diphtheroid.3 After menopause, circulating estrogen levels (mainly estradiol), are dramatically reduced from greater than 120 pg per mL to around 18 pg per mL.3 Numerous cytologic transformations follow estrogen reduction, including proliferation of connective tissue, fragmentation of elastin and hyalinization of collagen. These changes may result in granulation, fissures, ecchymoses, telangiectases and ulcerations.s Postmenopausal changes in tissue composition are not limited to the genital trail but also include the urinary tract because of the shared common embryologic

origin. Vaginal and urethral epithelia are estrogen dependent and adversely change in an estrogendeprived environment.

Predisposing Factors

Menopause is the leading cause of decreased levels of circulating estrogen; therefore, it is the etiology in almost all cases of atrophic vaginitis. In nonmenopausal women, production of ovarian estrogen can be interrupted by radiation therapy, chemotherapy, immunologic disorders and oophorectomy. The postpartum decline in estrogen levels accompanies the loss of placental estrogen and the antagonistic action of prolactin on estrogen production during lactation. Side effects of antiestrogen medications, including medroxyprogesterone (Provera), tamoxifen (Nolvadex), danazol (Danocrine), leuprolide (Lupron) and nafarelin (Synarel), are also implicated as causes of atrophic vaginitis 6 An increase in the severity of symptoms occurs in women who are naturally premenopausally estrogen deficient, smoke cigarettes, have not given birth vaginally or exhibit nonfluctuating levels of estrogen.3,7,8 Milder atrophy occurs in postmenopausal women who participate in coitus, have higher androgen levels and have not undergone vaginal surgery (Table 1).3,6-9

Presenting Signs and Symptoms

A long-term decrease in estrogen stimulation is generally required before symptoms of atrophic vaginitis arise. A decrease in vaginal lubrication is an early hallmark of hormone insufficiency." Genital symptoms include dryness, burning, dyspareunia, loss of vaginal secretions, leukorrhea, vulvar pruritus, feeling of pressure, itching and yellow malodorous discharge.3,6,11 Urinary symptoms of urethral discomfort, frequency, hematuria, urinary tract infection, dysuria and stress incontinence may be later symptoms of vaginal atrophy (Table 2).3,6,10,11 All atrophic vaginitis symptoms can be exacerbated by a simultaneous infection of candidiasis, trichomoniasis or bacterial vaginosis. Over time, the lack of vaginal lubrication often results in sexual dysfunction and associated emotional distress.

Diagnosis

PHYSICAL EXAMINATION

It is important not to assume a diagnosis of atrophic vaginitis (or solely a diagnosis of atrophic vaginitis) in the postmenopausal patient who presents with urogenital complaints. A patient history should include attention to exogenous agents that may cause or further aggravate symptoms. Perfumes, powders, soaps, deodorants, panty liners, spermicides and lubricants often contain irritant compounds 6 In addition, tight-fitting clothing and long-term use of perineal pads or synthetic materials can worsen atrophic symptoms12 (Table 3) 6,12

On examination, several signs of vaginal atrophy will be evident. Atrophic epithelium appears pale, smooth and shiny. Often, inflammation with patchy erythema, petechiae and increased friability may be present. External genitalia should be examined for diminished elasticity, turgor of skin, sparsity of pubic hair, dryness of labia, vulvar dermatoses, vulvar lesions and fusion of the labia minora3,6 (Figure 1). Introital stenosis to a width less then two fingers and decreased vaginal depth will be apparent; if these conditions are not diagnosed before insertion of the speculum, the pelvic examination will cause considerable pain. Friable and poorly rugated vaginal epithelium is more prone to traumatic damage. Ecchymoses and minor lacerations at peri-introital and posterior fourchette may also recur after coitus or during a speculum examination. Vaginal examination or sexual activity can result in vaginal bleeding or spotting. Vulvar signs of irritation caused by urinary incontinence may also be identified on pelvic examination. Cystocele, urethral polyps, urethral caruncle, eversion of urethral mucosa, pelvic organ prolapse and rectocele often

accompany atrophic vaginitis3 (Table 4).3.6

LABORATORY FINDINGS

Laboratory diagnostic testing, including serum hormone levels and Papanicolaou smear, can confirm the presence of urogenital atrophy (Figures 2 and 3, Table 5).3,13 Cytologic examination of smears from the upper one third of the vagina show an increased proportion of parabasal cells and a decreased percentage of superficial cells. An elevated pH level (postmenopausal pH levels exceeding 5),3 monitored by a pH strip in the vaginal vault, may also be a sign of vaginal atrophy. In addition, a vaginal ultrasonogram of the uterine lining that demonstrates a thin endometrium measuring between 4 and 5 mm signifies loss of adequate estrogenic stimulation.13 On microscopic evaluation, loss of superficial cells is obvious with atrophy, but there may also be evidence of infection with Trichomonas, candida or bacterial vaginitis.

Treatment

ESTROGEN REPLACEMENT

Because the lack of circulating, natural estrogens is the primary cause of atrophic vaginitis, hormone replacement therapy is the most logical choice of treatment and has proved to be effective in the restoration of anatomy and the resolution of symptoms. Estrogen replacement restores normal pH levels and thickens and revascularizes the epithelium. Adequate estrogen replacement therapy increases the number of superficial cells.3 Estrogen therapy may alleviate existing symptoms or even prevent development of urogenital symptoms if initiated at the time of menopause. Contraindications to estrogen therapy include estrogen-sensitive tumors, end-stage liver failure and a past history of estrogen-related thromboembolization. Adverse effects of estrogen therapy include breast tenderness, vaginal bleeding and a slight increase in the risk of an estrogen-dependent neoplasm.14 An increased risk of developing endometrial carcinoma and hyperplasia is conclusively related to unopposed, exogenous estrogen intake.15 Factors that determine the degree of increased risk include duration, dosage and method of estrogen delivery. Routes of administration include oral, transdermal and intravaginal. Dose frequency may be continuous, cyclic or symptomatic. The amount of estrogen and the duration of time required to eliminate symptoms depend greatly on the degree of vaginal atrophy and vary among patients.

Systemic administration of estrogen has been shown to have a therapeutic effect on symptoms of atrophic vaginitis. Additional advantages of systemic administration include a decrease in postmenopausal bone loss and alleviation of vasomotor dysfunction (hot flushes). Standard dosages of systemic estrogen, however, may not eliminate the symptoms of atrophic vaginitis in 10 to 25 percent of patients.16 Systemic estrogen in higher dosages may be necessary to alleviate symptoms. Some women require coadministration of a vaginal estrogen product that is applied locally. Up to 24 months of therapy may be necessary to totally eradicate dryness; however, some patients do not fully respond even to this treatment regimen.10

Other treatment options include transvaginal delivery of estrogen in the form of creams, pessaries or a hormone-releasing ring (Estring). Treatment with a low-dose transvaginal estrogen has proved effective in relieving symptoms without causing significant proliferation of the vaginal epithelium.2,12,14,17 The genitourinary pH level is also lowered, leading to a decreased incidence of urinary tract infections. Absorption rates increase with treatment duration because of the enhanced vascularity of the treated epithelium. The advantage of transvaginal treatment may be a decreased risk of endometrial carcinoma because a lower hormone amount is required to eliminate urogenital symptoms. Negative effects of transvaginal treatment include patient dislike of vaginal manipulation, less prevention of postmenopausal bone loss and vasomotor dysfunction, decreased control of absorption with vaginal creams compared to oral and transdermal delivery, and irregular treatment intervals that may cause patients to forget to

administer the treatment.6

Transvaginal rings offer convenience, constancy of hormonal concentration in the blood stream and a therapeutic value equivalent to creams without the need for frequent application. Control of hormone dosage is manipulated by changing the surface area of the ring. Atrophic vaginitis symptoms are relieved (with a dosage of 5 to 10 pg per 24 hours) without stimulation of endometrial proliferation, thereby eliminating the need to add opposing progestogen to the regimen.18 Rings may be removed and reinserted by most patients with little difficulty and can be worn during coitus.

MOISTURIZERS AND LUBRICANTS

Moisturizers and lubricants may be used in conjunction with estrogen replacement therapy or as alternative treatments. 17 Some patients choose not to take hormone replacement, or they may have medical contraindications or experience hormonal side effects. Patients who wish to avoid using estrogen should not use moisturizers that contain ginseng because they may have estrogenic properties.19 Moisturizers help maintain natural secretions and coital comfort. The length of effectiveness is generally less than 24 hours.

Sexual Activity

Sexual activity is a healthful prescription for postmenopausal women who have a substantially estrogenized vaginal epithelium. It has been shown to encourage vaginal elasticity and pliability, and the lubricative response to sexual stimulation. Women who participate in sexual activity report fewer symptoms of atrophic vaginitis and, on vaginal examination, have less evidence of stenosis and shrinkage in comparison with sexually inactive women. A negative relationship exists between coital activity, including masturbation, and symptoms of vaginal atrophy.9

Because no positive relationship has been shown to exist between estrogen levels and sexual activity, coitus is not hypothesized to restore or maintain estrogen in postmenopausal women. The existence of a positive relationship between coital activities and both gonadotropins and androgens indicates the importance of these compounds to healthy vaginal epithelium when estrogen levels are decreased 9 All sexually active women should take appropriate precautions against sexually transmitted diseases, including the human immunodeficiency virus.

Final Comment

Vaginal atrophy need not be an inevitable consequence of menopause or other events that result in long-term estrogen loss. Active diagnosis and intervention may prevent development of atrophic vaginitis or eliminate existing symptoms. Awareness of the many choices for delivery of estrogen replacement, as well as alternative therapies, greatly increases a physician's ability to prescribe treatment that is compatible with a patients physical needs and lifestyle. In the appropriate circumstances, encouragement of sexual activity is also an important source of nonpharmacologic treatment about which many patients may not be informed. Ironically, continued coital relations may enhance a woman's ability to enjoy a healthy sex life after menopause by encouraging maintenance of a physiologic environment defensive to atrophic changes.

Figures 2 and 3 provided by Renee Artymyshyn, M.D., associate professor Department of Pathology and Salim Haddad, M.D., senior resident, Department of Pathology, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick.

[Sidebar]

TABLE 1

Factors That Increase the Risk of Developing Atrophic Vaginitis

Menopause
Decreased ovarian functioning
Radiation therapy
Chemotherapy
Immune disorder
Oophorectomy
Postpartum loss of placental estrogen
Elevated prolactin level during lactation
Medications containing antiestrogen properties6
Tamoxifen (Nolvadex)
Danazol (Danocrine)
Medroxyprogesterone (Provera)
Leuprolide (Lupron)
Nafarelin (Synarel)
Natural estrogen deficiency before menopause3
Cigarette smoking'
Vaginal nulliparity
Nonfluctuating estrogen levels8
Cessation of coital activity9
Information from references 3 and 6 through 9.
TABLE 2
Presenting Symptoms of Atrophic Vaginitis Genital
Dryness
Itching
Burning
Dyspareunia
Burning leukorrhea
Vulvar prutitus
Feeling of pressure
Yellow malodorous dischare
Urinary
Dysuria
Hematuria
Urinary frequency
Urinary tract infection
Stress incontinence
Information from references 3,6,10 and 11.

[Sidebar]

TABLE 3
Differential Diagnosis of Atrophic Vaginitis Candidiasis
Bacterial vaginosis
Trichomoniasis
Contract irritation ir reaction to:
Perfumes
Powders
Deodorants
Panty liners
Perineal pads
Soaps
Spermicides
Libricants
Tight-fitting or synthetic clothing
Information from Beard MK. Atrophic vaginitis. Can it be prevented as well as treated? Postgrad Med 1992;91:257-60, and Beard MK, Curtis LR. Libido, menopause, and estrogen replacement therapy. Postgrad Med 1989;86:225-8.

[Sidebar]

TABLE 4
Physical Signs of Atrophic Vaginitis
Genital
Pale, smooth or shiny vaginal epithelium
Loss of elasticity or turgor of skin
Sparsity of public hair
Dryness of labia
Fusion of labia minora
Introital stenosis
Friable, unrugated epithelium
Pelvic organ prolapse
Rectocele
Vulvar dermatoses
Vulvar lesions
Vulvar patch erythema

Petechiae of epithelium
Utethreal
Urethral caruncle
Eversion of urethral mucosa
Cystocele
Urethral polyps
Ecchymoses
Minor lacerations at peri-introital and posterior fourchette
Information from Pandit L, Ouslander JG. Postmenopausal vaginal atrophy and atrophic vaginitis. Am J Med Sci 1997,'314:228-31, and Beard MK. Atrophic vaginitis. Can it be prevented as well as treated? Postgrad Med 1992;91:257-60.

[Reference]
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Froudarakis G, Hassan E, et al. Cigarette smoking and vaginal atrophy in postmenopausal women. In Vivo 1996;10:597-600.

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atrophic vaginitis with low-dose oestradiol vaginal tablets. Maturitas 1991;14:23-31.
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18. Smith P, Heimer G, Lindskog M, Ulmsten U. Oestradiol-releasing vaginal ring for treatment of postmenopausal urogenital atrophy. Maturitas 1993; 16:145-54.
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NICOLE S. NEVADUNSKY is a research assistant and medical student at the University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick.
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1: Acta Obstet Gynecol Scand 2000 Apr;79(4):293-7 Related Articles, Links

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Comparison of usefulness of estradiol vaginal tablets and estriol vagitories for treatment of vaginal atrophy.

Dugal R, Hesla K, Sordal T, Aase KH, Lilleeidet O, Wickstrom E.

Soebergtorget Legesenter, Sandefjord, Norway.

BACKGROUND: Atrophic vaginitis is a common condition. This study compared the usefulness of estradiol vaginal tablets (EVT) and estriol vagitories (EV) in treatment of atrophic vaginitis. METHODS: Ninety-six postmenopausal women with symptoms of atrophic vaginitis were treated for 24 weeks with either EVT or with EV. Patients used the medication daily for the first 2 weeks of the study, and twice-weekly thereafter. RESULTS: Both EVT and EV were effective in treating vaginal atrophy and patients in both treatment groups experienced a significant improvement in vaginal symptoms such as itching, irritation, dryness, and dyspareunia. At the end of the study three (6%) EVT treated women reported leakage and none needed to use sanitary towels. Among the EV treated women 31 (65%) reported leakage and 14 (29%) required sanitary protection. Furthermore, 90% in the EVT group perceived the medication as hygienic compared to 79% in the EV group, and 49% in the EVT group indicated that the product was easy to use compared to 28% in the EV group. Endometrial thickness was increased (1.1 mm with EVT and 0.5 mm on EV) in both treatment groups during the first 2 weeks of the study, but returned to baseline levels when the frequency of drug application was reduced to twice-weekly. CONCLUSIONS: Estradiol vaginal tablets provides an effective alternative to traditional forms of local estrogen therapy.

Publication Types:
- Clinical Trial
- Multicenter Study
- Randomized Controlled Trial

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L5 ANSWER 42 OF 46 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1973:143937 CAPLUS
DOCUMENT NUMBER: 78:143937
TITLE: Comparative trial of P1496, a new nonsteroidal estrogen analog
AUTHOR(S): Utian, Wulf H.
CORPORATE SOURCE: Dep. Gynaecol., Groote Schuur Hosp., Cape Town, S. Afr.
SOURCE: Brit. Med. J. (1973), 1(5853), 579-81
CODEN: BMJOAE
DOCUMENT TYPE: Journal
LANGUAGE: English
AB P1496 (I) [26538-44-3] at 75 mg/day and conjugated equine **estrogens** at 1.25 mg/day given orally to hysterectomized women were equally effective in significantly decreasing the incidence and severity of symptoms assocd. with endogenous **estrogen** withdrawal (hot flashes and **atrophic vaginitis**). I also significantly decreased plasma calcium [7440-70-2] level. Neither estrogen affected serum protein-bound I, packed cell vol. or Hb, or plasma cholesterol, P, or alk. phosphatase.
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L5 ANSWER 43 OF 46 MEDLINE
ACCESSION NUMBER: 71035215 MEDLINE
DOCUMENT NUMBER: 71035215 PubMed ID: 5480497
TITLE: **Estrogen** therapy in **atrophic vaginitis**.
AUTHOR: Kyriazis G A; Balin H
SOURCE: PENNSYLVANIA MEDICINE, (1970 Dec) 73 (12) 32-4.
Journal code: 0045606. ISSN: 0031-4595.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
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ENTRY MONTH: 197101
ENTRY DATE: Entered STN: 19900101
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TI **Estrogen** therapy in **atrophic vaginitis**.

L5 ANSWER 44 OF 46 MEDLINE
ACCESSION NUMBER: 69066802 MEDLINE
DOCUMENT NUMBER: 69066802 PubMed ID: 5727825
TITLE: **Atrophic vaginitis** treated with nitrofurazone-**estrogen** vaginal suppositories.
AUTHOR: Kearns P R; Stewart R H; Mendel E B
SOURCE: JOURNAL OF THE LOUISIANA STATE MEDICAL SOCIETY, (1968 Nov) 120 (11) 457-60.
Journal code: 7505618. ISSN: 0024-6921.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 196902

ENTRY DATE: Entered STN: 19900101
Last Updated on STN: 19900101
Entered Medline: 19690207
TI **Atrophic vaginitis** treated with nitrofurazone-
estrogen vaginal suppositories.

L5 ANSWER 45 OF 46 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1969:34448 BIOSIS
DOCUMENT NUMBER: BR05:34448
TITLE: **ATROPHIC VAGINITIS** TREATED WITH
NITROFURAZONE ANTI INFECT **ESTROGEN** VAGINAL
SUPPOSITORIES WOMAN DI ETHYL STILBESTROL HORMONE.
AUTHOR(S): KEARNS P R; STEWART R H; MENDEL E B
SOURCE: J. La. State Med. Soc., (1968) 120 (1), 457-460.
CODEN: JLSMAW. ISSN: 0024-6921.
FILE SEGMENT: BR; OLD
LANGUAGE: Unavailable
TI **ATROPHIC VAGINITIS** TREATED WITH NITROFURAZONE ANTI
INFECT **ESTROGEN** VAGINAL SUPPOSITORIES WOMAN DI ETHYL STILBESTROL
HORMONE.

L5 ANSWER 46 OF 46 MEDLINE
ACCESSION NUMBER: 65145932 MEDLINE
DOCUMENT NUMBER: 65145932
TITLE: NITROFURAZONE-**ESTROGEN** VAGINAL SUPPOSITORIES IN
THE TREATMENT OF **ATROPHIC VAGINITIS**.
AUTHOR: FRIEDMAN J A; OLSEN N
SOURCE: JOURNAL OF THE AMERICAN GERIATRICS SOCIETY, (1965 SEP) 13
828-31.
ISSN: 0002-8614.
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DOCUMENT TYPE: Journal
LANGUAGE: English
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ATROPHIC VAGINITIS.

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L5 ANSWER 21 OF 46 MEDLINE
ACCESSION NUMBER: 93342960 MEDLINE
DOCUMENT NUMBER: 93342960 PubMed ID: 8393609
TITLE: Estrogens and the urogenital tract. Studies on steroid hormone receptors and a clinical study on a new estradiol-releasing vaginal ring.
AUTHOR: Smith P
CORPORATE SOURCE: Department of Obstetrics and Gynecology, University Hospital, Uppsala, Sweden.
SOURCE: ACTA OBSTETRICIA ET GYNECOLOGICA SCANDINAVICA. SUPPLEMENT, (1993) 157 1-26.
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PUB. COUNTRY: Denmark
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AB **Estrogen** receptors and progesterone receptors were detected and quantified in female pelvic floor muscles, urogenital ligaments and in uterus (myometrium) by use of monoclonal antibody assay techniques. Qualitative assessment with immunohistochemical methods further localized the **estrogen** receptors and progesterone receptors to the nuclei of connective tissue cells and striated muscle cells in the levator ani muscle, and to the cell nuclei of smooth muscle cells in the round ligament. These findings fulfil a prerequisite for viewing the pelvic floor and the round ligament as target organs for **estrogens**. The results also contribute to the understanding of the etiological role the reduction in **estrogen** levels has on the increased incidence of prolapse and urinary incontinence after the menopause. For treatment of urogenital mucosal atrophy a new vaginal silicone ring releasing 5-10 micrograms **estradiol**/24 h for a minimum of 90 days has been developed. The efficacy, safety and acceptability of the ring were studied in 222 postmenopausal women with symptoms and signs of atrophic vaginal mucosa. The maturation of the vaginal epithelium, as measured by cytological parameters, was significantly improved during treatment. There were significant decreases in vaginal pH, and these changes correlated well with the cytological evaluation. No proliferation of the endometrium was encountered. The therapy had a significant effect on symptoms and on signs of **atrophic vaginitis**, with cure/improvement registered in > or = 90%. The patient acceptability was high. It is concluded that a vaginal silicone ring giving a continuous release of an ultra-low dose of **estradiol** is an effective and safe treatment for urogenital **estrogen** deficiency. No addition of progestogen is needed.

AB **Estrogen** receptors and progesterone receptors were detected and quantified in female pelvic floor muscles, urogenital ligaments and in uterus (myometrium) by use of monoclonal antibody assay techniques. Qualitative assessment with immunohistochemical methods further localized the **estrogen** receptors and progesterone receptors to the nuclei of connective tissue cells and striated muscle cells in the levator ani muscle,. . . round ligament. These findings fulfil a prerequisite for viewing the pelvic floor and the round ligament as target organs for **estrogens**. The results also contribute to the understanding of the etiological role the reduction in **estrogen** levels has on the increased incidence of prolapse and urinary incontinence after the menopause. For treatment of urogenital mucosal atrophy a new vaginal silicone ring releasing 5-10 micrograms **estradiol**/24 h for a minimum of 90 days has been developed. The efficacy, safety and

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ACCESSION NUMBER: 1993:484159 BIOSIS
DOCUMENT NUMBER: PREV199396117759
TITLE: Estrogens and the urogenital tract: Studies on steroid hormone receptors and a clinical study on a new estradiol releasing vaginal ring.
AUTHOR(S): Smith, Peter
CORPORATE SOURCE: Dep. Obstet. Gynecol., Univ. Hosp., S-751 85 Uppsala Sweden
SOURCE: Acta Obstetricia et Gynecologica Scandinavica, (1993) Vol. 72, No. 157 SUPPL., pp. 1-26.
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DOCUMENT TYPE: Article
LANGUAGE: English

AB **Estrogen** receptors and progesterone receptors were detected and quantified in female pelvic floor muscles, urogenital ligaments and in uterus (myometrium) by use of monoclonal antibody assay techniques. Qualitative assessment with immunohistochemical methods further localized the **estrogen** receptors and progesterone receptors to the nuclei of connective tissue cells and striated muscle cells in the levator ani muscle, and to the cell nuclei of smooth muscle cells in the round ligament. These findings fulfil a prerequisite for viewing the pelvic floor and the round ligament as target organs for **estrogens**. The results also contribute to the understanding of the etiological role in reduction in **estrogen** levels has on the increased incidence of prolapse and urinary incontinence after the menopause. For treatment of urogenital mucosal atrophy a new vaginal silicone ring releasing 5-10 mu-g **estradiol**/24 h for a minimum of 90 days has been developed. The efficacy, safety and acceptability of the ring were studied in 222 postmenopausal women with symptoms and signs of atrophic vaginal mucosa. The maturation of the vaginal epithelium, as measured by cytological parameters, was significantly improved during treatment. There were significant decreases in vaginal pH, and these changes correlated well with the cytological evaluation. No proliferation of the endometrium was encountered. The therapy had a significant effect on symptoms and on signs of **atrophic vaginitis**, with cure/improvement registered in gtoreq 90%. The patient acceptability was high. It is concluded that a vaginal silicone ring giving a continuous release of an ultra-low dose of **estradiol** is an effective and safe treatment for urogenital **estrogen** deficiency. No addition of progestogen is needed.

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of 90 days has been developed. The efficacy, safety and acceptability of the ring were studied. . . evaluation. No proliferation of the endometrium was encountered. The therapy had a significant effect on symptoms and on signs of **atrophic vaginitis**, with cure/improvement registered in gtoreq 90%. The patient acceptability was high. It is concluded that a vaginal silicone ring giving a continuous release of an ultra-low dose of **estradiol** is an effective and safe treatment for urogenital **estrogen** deficiency. No addition of progestogen is needed.

L5 ANSWER 23 OF 46 MEDLINE
ACCESSION NUMBER: 93089247 MEDLINE
DOCUMENT NUMBER: 93089247 PubMed ID: 1360765
TITLE: Urinary incontinence in the elderly: pharmacologic therapies.
COMMENT: Comment in: Am Fam Physician. 1993 Oct;48(5):732
AUTHOR: Peggs J F
CORPORATE SOURCE: University of Michigan Medical School, Ann Arbor.
SOURCE: AMERICAN FAMILY PHYSICIAN, (1992 Dec) 46 (6) 1763-9. Ref: 13
Journal code: 1272646. ISSN: 0002-838X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199212
ENTRY DATE: Entered STN: 19930129
Last Updated on STN: 19950206
Entered Medline: 19921231

AB Treatment of acute urinary incontinence should be directed toward the underlying cause, such as infection, medication side effect, **atrophic vaginitis**, anxiety, depression and restricted mobility. Pharmacologic treatment depends on identification of one of the four subtypes of chronic urinary incontinence: stress, urge, overflow or mixed. Stress incontinence responds to alpha-adrenergic agents, which increase sphincter tone. Urge incontinence is the most common type of incontinence in the elderly; it can be treated with anticholinergic agents, smooth muscle relaxants, **estrogen** replacement therapy in women and, possibly, calcium antagonists. Overflow incontinence is caused by neurologic deficits, such as diabetes, or outflow obstruction, such as from prostatic enlargement, urethral stricture and tumors. Anticholinergic agents and alpha-adrenergic agents should be considered only after existing outflow obstruction is surgically corrected or intermittent catheterization is unsuccessful.

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L5 ANSWER 24 OF 46 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 92340803 MEDLINE
DOCUMENT NUMBER: 92340803 PubMed ID: 1634725
TITLE: Urinary tract infections and estrogen use in older women.
AUTHOR: Orlander J D; Jick S S; Dean A D; Jick H

CORPORATE SOURCE: Department of Veterans Affairs Medical Center, Boston University School of Medicine, Massachusetts.
CONTRACT NUMBER: FD-U-000071-10 (FDA)
SOURCE: JOURNAL OF THE AMERICAN GERIATRICS SOCIETY, (1992 Aug) 40 (8) 817-20.
Journal code: 7503062. ISSN: 0002-8614.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199208
ENTRY DATE: Entered STN: 19920911
Last Updated on STN: 19920911
Entered Medline: 19920827

AB OBJECTIVE: To examine the relationship between exogenous **estrogen** use and risk of clinically diagnosed urinary tract infection (UTI) in older women. DESIGN: A case-control study. SETTING: Two hundred seventy-six general practices. PATIENTS: Cases (n = 3,616) were women, age 50-69 years, with a first recorded UTI in the calendar years 1989 or 1990. Controls (n = 19,162) were matched for age and practice. MAIN OUTCOME MEASURE: Clinical diagnosis of UTI. RESULTS: Women using **estrogens** for greater than or equal to 1 year had an increased risk of being diagnosed with a UTI compared to non-users, crude odds ratio (OR) 1.9 (95% CI 1.5-2.2). All of this excess risk was observed in women with intact uteri, OR 2.1 (CI 1.7-2.7). Hysterectomized women had no increased risk, OR 1.1 (CI 0.8-1.5). Controlling for diabetes, neurologic deficit, **atrophic vaginitis**, incontinence, and age did not affect the observed associations. CONCLUSION: **Estrogen** use is associated with an increased risk of UTI in older women with intact uteri but not in hysterectomized women. This observed differential effect on women with or without uteri may be explained by prescribing biases between these two groups of women, but we lack any evidence to support this conclusion over several alternative possibilities.

AB OBJECTIVE: To examine the relationship between exogenous **estrogen** use and risk of clinically diagnosed urinary tract infection (UTI) in older women. DESIGN: A case-control study. SETTING: Two hundred. . . Controls (n = 19,162) were matched for age and practice. MAIN OUTCOME MEASURE: Clinical diagnosis of UTI. RESULTS: Women using **estrogens** for greater than or equal to 1 year had an increased risk of being diagnosed with a UTI compared to. . . uteri, OR 2.1 (CI 1.7-2.7). Hysterectomized women had no increased risk, OR 1.1 (CI 0.8-1.5). Controlling for diabetes, neurologic deficit, **atrophic vaginitis**, incontinence, and age did not affect the observed associations. CONCLUSION: **Estrogen** use is associated with an increased risk of UTI in older women with intact uteri but not in hysterectomized women.. . .

L5 ANSWER 25 OF 46 MEDLINE
ACCESSION NUMBER: 92253481 MEDLINE
DOCUMENT NUMBER: 92253481 PubMed ID: 1579532
TITLE: Atrophic vaginitis. Can it be prevented as well as treated?.
AUTHOR: Beard M K
CORPORATE SOURCE: Department of Obstetrics and Gynecology, LDS Hospital.
SOURCE: POSTGRADUATE MEDICINE, (1992 May 1) 91 (6) 257-60. Ref: 9
Journal code: 0401147. ISSN: 0032-5481.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 199206
ENTRY DATE: Entered STN: 19920619
Last Updated on STN: 19920619
Entered Medline: 19920609

AB **Atrophic vaginitis** is not only treatable but preventable. Because the vagina is an **estrogen**-dependent organ, the mainstay of management is **estrogen** replacement therapy, which should be initiated with the onset of ovarian decline at menopause or when a woman presents with symptoms of **atrophic vaginitis**. Lubricants and vaginal moisturizers may be useful adjuncts. Regular sexual activity is also helpful in maintaining a healthy, functional vagina.

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L5 ANSWER 26 OF 46 MEDLINE
ACCESSION NUMBER: 93113243 MEDLINE
DOCUMENT NUMBER: 93113243 PubMed ID: 1472888
TITLE: Vulvovaginitis in the postmenopausal woman.
AUTHOR: Peters N C
SOURCE: NURSE PRACTITIONER FORUM, (1992 Sep) 3 (3) 152-4.
Journal code: 9100939. ISSN: 1045-5485.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Nursing Journals
ENTRY MONTH: 199302
ENTRY DATE: Entered STN: 19930219
Last Updated on STN: 19930219
Entered Medline: 19930201

AB Determining the cause and appropriate treatment of vulvovaginitis in the postmenopausal woman is complicated by the effects of decreased endogenous **estrogen** as well as normal aging changes. The symptoms of vulvovaginitis remain the same at any age but after menopause these symptoms can be the result of atrophy alone. **Estrogen** is the treatment of choice for **atrophic vaginitis**. The differential diagnosis and treatment of sexually transmitted diseases, candidiasis, and vulvar dystrophies are described and various alternatives to **estrogen** use are included.

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=> d 11-16 ibib abs kwic
YOU HAVE REQUESTED DATA FROM FILE 'MEDLINE, CAPLUS, BIOSIS' - CONTINUE? (Y)/N:y

L5 ANSWER 11 OF 46 MEDLINE

ACCESSION NUMBER: 2000005067 MEDLINE
DOCUMENT NUMBER: 20005067 PubMed ID: 10535167
TITLE: [Hormone therapy and urogynecology].
Hormonalni lecba a urogynekologie.
AUTHOR: Halaska M; Raus K; Martan A; Voigt R
CORPORATE SOURCE: I. gynek.-porod. klinika 1. LF UK a VFN, Praha.
SOURCE: CESKA GYNEKOLOGIE, (1998 Nov) 63 (6) 453-6.
Journal code: 9423768. ISSN: 1210-7832.
PUB. COUNTRY: Czech Republic
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Czech
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991115

AB The female genital and urinary systems exists in close anatomical and functional proximity, disorders of one resulting in dysfunction of the other. The investigation and management of lower urinary tract disorders must take this important relationship into consideration, as neither can be viewed in isolation. The value of **estrogen** replacement therapy as a treatment of urinary incontinence is controversial and until today there is a little substantial evidence to conclude that **estrogen** therapy alone is of value in the treatment of this symptom. This conflicting evidence concerning the therapeutic benefit of **estrogen** therapy in stress urinary incontinence seems to be outweighed with other advantages of **estrogen** replacement therapy. Clear evidence exists to suggest that recurrent urinary tract infections can be prevented or even treated by the use of **estrogen** therapy. Systemic **estrogen** replacement appears to relieve the symptoms of urgency, urge incontinence, frequency, nycturia and dysuria, and low-dose topical **estrogen** is effective in the management of **atrophic vaginitis**. Even with postulating the HRT to be of enormous therapeutic value to postmenopausal women in urogynecology it may stay only a mean of support of other causal methods of treatment of dysfunction of lower urinary tract.

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L5 ANSWER 12 OF 46 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:625501 CAPLUS
DOCUMENT NUMBER: 127:272868
TITLE: Estrogens, antiestrogens, and the urogenital tract
AUTHOR(S): Kelleher, C. J.; Cardozo, Linda
CORPORATE SOURCE: King's College Hospital, London, UK
SOURCE: Estrogens and Antiestrogens (1997), 243-257.
Editor(s): Lindsay, Robert; Dempster, David W.; Jordan, V. Craig. Lippincott-Raven: Philadelphia, Pa.

CODEN: 65BSAY
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review, with 92 refs., on **estrogen** deficiency and urogenital symptoms, physiol. of urogenital atrophy; physiol. of **estrogens** and urinary incontinence; epidemiol. of urogenital atrophy and urinary incontinence; **estrogen** therapy for **atrophic vaginitis**; **estrogen** therapy for urinary incontinence; **estrogens** in the treatment of recurrent urinary tract infection; antiestrogens and the urogenital tract; and effects of progesterone and progestogens on the urinary tract.
AB A review, with 92 refs., on **estrogen** deficiency and urogenital symptoms, physiol. of urogenital atrophy; physiol. of **estrogens** and urinary incontinence; epidemiol. of urogenital atrophy and urinary incontinence; **estrogen** therapy for **atrophic vaginitis**; **estrogen** therapy for urinary incontinence; **estrogens** in the treatment of recurrent urinary tract infection; antiestrogens and the urogenital tract; and effects of progesterone and progestogens on the urinary tract.

L5 ANSWER 13 OF 46 MEDLINE
ACCESSION NUMBER: 1998009756 MEDLINE
DOCUMENT NUMBER: 98009756 PubMed ID: 9349043
TITLE: The role of vaginal estrogen in the treatment of urogenital dysfunction in postmenopausal women.
AUTHOR: Bernier F; Jenkins P
CORPORATE SOURCE: Continence Education Program, Colorado Gynecology and Continence Center, Denver, USA.
SOURCE: UROLOGIC NURSING, (1997 Sep) 17 (3) 92-5. Ref: 23
Journal code: 8812256. ISSN: 1053-816X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Nursing Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971212
AB Decreased **estrogen** levels result in significantly lower urogenital tract changes and adversely influences quality of life. Consequences include **atrophic vaginitis**, atrophic urethritis, urinary incontinence, and pelvic organ prolapse. Evaluation of lower genital tract **estrogen** status is an integral part of evaluating the postmenopausal woman with urogenital symptoms.
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L5 ANSWER 14 OF 46 MEDLINE
ACCESSION NUMBER: 1998009755 MEDLINE
DOCUMENT NUMBER: 98009755 PubMed ID: 9349042
TITLE: Estrogen in urinary incontinence treatment: an anatomic and physiologic approach.
AUTHOR: Maloney C
CORPORATE SOURCE: Seton Center for Ambulatory Care, Troy, New York, USA.
SOURCE: UROLOGIC NURSING, (1997 Sep) 17 (3) 88-91. Ref: 14
Journal code: 8812256. ISSN: 1053-816X.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Nursing Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971212

AB Most women and health care providers are knowledgeable about the benefits that **estrogen** replacement therapy has on the prevention of cardiovascular disease and osteoporosis. What is commonly unknown and under research is the role **estrogen** plays in maintaining continence. The lower urinary tract shares a common embryologic origin with the female genital organs and is hormonally sensitive. Menopause, either surgical or natural, results in decreased or diminished circulating **estrogens** that can affect the genitourinary system, causing atrophic symptoms. A comprehensive urinary incontinence workup should include assessment of the vaginal mucosa and treatment of hormone deficiency symptoms such as **atrophic vaginitis** and urethritis. Risk assessment should be done before hormone replacement therapy is considered.

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L5 ANSWER 15 OF 46 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 97184979 MEDLINE
DOCUMENT NUMBER: 97184979 PubMed ID: 9032748
TITLE: Vaginal ultrasound of the endometrium in postmenopausal women with symptoms of urogenital atrophy on low-dose estrogen or tibolone treatment: a comparison.
AUTHOR: Botsis D; Kassanos D; Kalogirou D; Antoniou G; Vitoratos N; Karakitsos P
CORPORATE SOURCE: Second Department of Obstetrics and Gynecology, Athens University, Greece.
SOURCE: MATURITAS, (1997 Jan) 26 (1) 57-62.
Journal code: 7807333. ISSN: 0378-5122.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970514
Last Updated on STN: 19970514
Entered Medline: 19970507

AB OBJECTIVE: The objective of this study was to compare the efficacy of locally administered low-dose **estrogens** (0.625 mg of conjugated **estrogens**) and orally administered tibolone in postmenopausal

women with symptoms and signs of **atrophic vaginitis**. Vaginal ultrasound was performed for the evaluation of endometrial or ovarian abnormalities. METHODS: A 6-month comparative randomised prospective study of women taking tibolone and locally administered low-dose **estrogens**. Seventy two postmenopausal women with symptoms of **atrophic vaginitis** were examined with vaginal ultrasound. The endometrial thickness, the endometrial volume, the uterus and the ovaries were measured before and after 6 months of treatment with low-dose **estrogens** or tibolone. RESULTS: In group A (low-dose **estrogens** treatment) the mean endometrial thickness, before and after treatment, was 3.0 +/- 0.1 mm and 2.9 +/- 0.8 mm, respectively. The mean ovarian volume was 3.9 ml. There were no changes in uterine volume during the treatment period. In group B (treated with tibolone) endometrial thickness was 3.2 +/- 0.3 mm and 3.2 +/- 0.7 mm, respectively. One women experienced vaginal bleeding. The volume of corpus uteri was unchanged after treatment. The volume of both ovaries was 4.2 ml and 3.9 ml, respectively. The overall acceptability of both types of administration was good. CONCLUSIONS: This study, using vaginal ultrasound, has shown that either hormone replacement therapy with tibolone or symptomatic treatment with low-dose **estrogens**, gives no sign of endometrial proliferation measured as endometrial thickness.

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L5 ANSWER 16 OF 46 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 97014250 MEDLINE
DOCUMENT NUMBER: 97014250 PubMed ID: 8861085
TITLE: Transvaginal sonography in postmenopausal women treated with low-dose estrogens locally administered.
AUTHOR: Botsis D; Kassanos D; Antoniou G; Vitoratos N; Zourlas P A
CORPORATE SOURCE: 2nd Department of Obstetrics and Gynecology, Athens University, Areteion Hospital, Athens, Greece.
SOURCE: MATURITAS, (1996 Feb) 23 (1) 41-5.
Journal code: 7807333. ISSN: 0378-5122.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 19970219
Entered Medline: 19970123

AB OBJECTIVE: The objective of this study was to determine the efficacy of low-dose **estrogens**, administered locally, in postmenopausal women with symptoms and signs of **atrophic vaginitis**. Transvaginal ultrasonography was performed for the evaluation of

endometrial or ovarian abnormalities. MATERIALS AND METHODS: Fifty-six healthy postmenopausal women with symptoms of **atrophic vaginitis** due to **estrogen** deficiency were examined with transvaginal ultrasound. The endometrial thickness, the uterus and the ovaries were measured before and after 6 months of treatment with low-dose **estrogens**. RESULTS: The mean endometrial thickness, before and after treatment was 3.1 +/- 0.8 mm and 3.1 +/- 1.2 mm respectively. The mean ovarian volume before treatment was 4.5 ml and there was no difference after treatment. There were no changes in uterine thickness during the treatment period. CONCLUSIONS: Our study, using transvaginal ultrasonography, has shown that low-dose **estrogens**, administered locally, give no sign of endometrial proliferation, measured as endometrial thickness, and do not alter the ovarian volume in postmenopausal volume.

AB OBJECTIVE: The objective of this study was to determine the efficacy of low-dose **estrogens**, administered locally, in postmenopausal women with symptoms and signs of **atrophic vaginitis**. Transvaginal ultrasonography was performed for the evaluation of endometrial or ovarian abnormalities. MATERIALS AND METHODS: Fifty-six healthy postmenopausal women with symptoms of **atrophic vaginitis** due to **estrogen** deficiency were examined with transvaginal ultrasound. The endometrial thickness, the uterus and the ovaries were measured before and after 6 months of treatment with low-dose **estrogens**. RESULTS: The mean endometrial thickness, before and after treatment was 3.1 +/- 0.8 mm and 3.1 +/- 1.2 mm respectively.. . . were no changes in uterine thickness during the treatment period. CONCLUSIONS: Our study, using transvaginal ultrasonography, has shown that low-dose **estrogens**, administered locally, give no sign of endometrial proliferation, measured as endometrial thickness, and do not alter the ovarian volume in. . .

=> d 17-20 ibib abs kwic
YOU HAVE REQUESTED DATA FROM FILE 'MEDLINE, CAPLUS, BIOSIS' - CONTINUE? (Y)/N:y

L5 ANSWER 17 OF 46 MEDLINE
ACCESSION NUMBER: 95406699 MEDLINE
DOCUMENT NUMBER: 95406699 PubMed ID: 7676260
TITLE: The aetiology of postmenopausal bleeding--a study of 163 consecutive cases in Singapore.
AUTHOR: Lee W H; Tan K H; Lee Y W
CORPORATE SOURCE: Department of Maternal Foetal Medicine, Kandang Kerbau Hospital, Singapore.
SOURCE: SINGAPORE MEDICAL JOURNAL, (1995 Apr) 36 (2) 164-8. Journal code: 0404516. ISSN: 0037-5675.
PUB. COUNTRY: Singapore
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199510
ENTRY DATE: Entered STN: 19951026
Last Updated on STN: 19951026
Entered Medline: 19951013

AB OBJECTIVE: To study the aetiology and pattern of Postmenopausal Bleeding (PMB) in the local population. DESIGN: A retrospective study SUBJECTS: 163 consecutive patients who presented with postmenopausal bleeding (PMB) SETTING: Kandang Kerbau Hospital, Singapore RESULTS: Malignant causes were found in 42 (25.7%) patients. Cervical carcinoma was the most common malignancy (12.9% of the patients) followed by endometrial carcinoma (11%). Important benign causes are cervicitis (12.9%), **atrophic**

vaginitis (12.3%) and cervical polyp (6.7%). Other benign causes include endometrial hyperplasia (3.1%), urethral caruncle (2.5%) and **estrogen** replacement therapy (1.8%). CONCLUSION: PMB is a symptom of varied aetiologies. The associated incidence of malignancy is high and a thorough diagnostic evaluation is mandatory.

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L5 ANSWER 18 OF 46 MEDLINE
ACCESSION NUMBER: 95313596 MEDLINE
DOCUMENT NUMBER: 95313596 PubMed ID: 7793304
TITLE: Sex hormones, the menopause and urinary problems.
AUTHOR: Cardozo L D; Kelleher C J
CORPORATE SOURCE: Department of Urogynaecology, King's College Hospital, London, UK.
SOURCE: GYNECOLOGICAL ENDOCRINOLOGY, (1995 Mar) 9 (1) 75-84. Ref: 66
Journal code: 8807913. ISSN: 0951-3590.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199507
ENTRY DATE: Entered STN: 19950807
Last Updated on STN: 19950807
Entered Medline: 19950725

AB To date, there have been few appropriate placebo-controlled studies using both subjective and objective parameters to assess the efficacy of **estrogen** therapy for the treatment of urinary incontinence. Further confusion arises from the heterogeneity of different study protocols. Consequently, the best treatment in terms of type and dose of **estrogen** and route of administration is unknown. From these studies, however, there is clear evidence to suggest that recurrent urinary tract infection can be prevented or even treated by the use of **estrogen** therapy. Furthermore, systemic **estrogen** replacement appears to alleviate the symptoms of urgency, urge incontinence, frequency, nocturia and dysuria, and low-dose topical **estrogen** is effective in the management of **atrophic vaginitis**. Although the latter example appears to be free from side-effects, even following prolonged administration, it is unclear whether low-dose therapy has a sufficient effect on the lower urinary tract to treat urinary incontinence. There is no conclusive evidence that **estrogen** replacement alone is sufficient to cure stress incontinence, but in combination with an alpha-adrenergic agonist there may be a role for **estrogen** therapy in the conservative management of genuine stress incontinence. On the other hand, **estrogen** supplementation definitely improves the quality of life of many postmenopausal women and, therefore, makes them better able to cope with other disabilities. Perhaps the role of **estrogen** in the management of postmenopausal urinary disorders is as an adjunct to other methods of treatment such as surgery, physiotherapy and drugs. This is certainly a hypothesis which should be tested.

AB To date, there have been few appropriate placebo-controlled studies using both subjective and objective parameters to assess the efficacy of **estrogen** therapy for the treatment of urinary incontinence.

Further confusion arises from the heterogeneity of different study protocols. Consequently, the best treatment in terms of type and dose of **estrogen** and route of administration is unknown. From these studies, however, there is clear evidence to suggest that recurrent urinary tract infection can be prevented or even treated by the use of **estrogen** therapy. Furthermore, systemic **estrogen** replacement appears to alleviate the symptoms of urgency, urge incontinence, frequency, nocturia and dysuria, and low-dose topical **estrogen** is effective in the management of **atrophic vaginitis**. Although the latter example appears to be free from side-effects, even following prolonged administration, it is unclear whether low-dose therapy has a sufficient effect on the lower urinary tract to treat urinary incontinence. There is no conclusive evidence that **estrogen** replacement alone is sufficient to cure stress incontinence, but in combination with an alpha-adrenergic agonist there may be a role for **estrogen** therapy in the conservative management of genuine stress incontinence. On the other hand, **estrogen** supplementation definitely improves the quality of life of many postmenopausal women and, therefore, makes them better able to cope with other disabilities. Perhaps the role of **estrogen** in the management of postmenopausal urinary disorders is as an adjunct to other methods of treatment such as surgery, physiotherapy. . .

L5 ANSWER 19 OF 46 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 96371951 MEDLINE
DOCUMENT NUMBER: 96371951 PubMed ID: 8775774
TITLE: Estrogen therapy in the management of problems associated with urogenital ageing: a simple diagnostic test and the effect of the route of hormone administration.
AUTHOR: Notelovitz M
CORPORATE SOURCE: Women's Medical and Diagnostic Center, Gainesville, FL 32607, USA.
SOURCE: MATURITAS, (1995 Dec) 22 Suppl S31-3.
Journal code: 7807333. ISSN: 0378-5122.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961025
Last Updated on STN: 19961025
Entered Medline: 19961016

AB **Estrogen** deficient women are prone to problems such as vaginal dryness, dyspareunia and a predilection to recurrent urinary tract infections and urinary incontinence. A preliminary double-blinded study in 67 symptomatic postmenopausal women confirmed: (1) that **atrophic vaginitis** is associated with an increase in the lateral wall vaginal pH; (2) this is paralleled by similar changes in pH in the urethra; (3) locally applied vaginal conjugated **estrogen** cream normalizes the pH in the vagina and urethra. Thus, the testing of the vaginal pH serves both as a surrogate for evaluating urethral pH and as a monitor of compliance with treatment.
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vaginal pH serves both as a. . .

L5 ANSWER 20 OF 46 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 94316379 MEDLINE
DOCUMENT NUMBER: 94316379 PubMed ID: 8041532
TITLE: Vaginal administration of low-dose conjugated estrogens: systemic absorption and effects on the endometrium.
AUTHOR: Handa V L; Bachus K E; Johnston W W; Robboy S J; Hammond C B
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, North Carolina.
SOURCE: OBSTETRICS AND GYNECOLOGY, (1994 Aug) 84 (2) 215-8.
Journal code: 0401101. ISSN: 0029-7844.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199408
ENTRY DATE: Entered STN: 19940905
Last Updated on STN: 19940905
Entered Medline: 19940825

AB OBJECTIVE: To test the hypothesis tha a very-low-dose regimen of vaginal **estrogen** would provide effective relief from **atrophic vaginitis** without endometrial proliferation. METHODS: Twenty postmenopausal women with symptoms, signs, and cytologic evidence of **atrophic vaginitis** were enrolled. Each subject was treated with 0.3 mg of conjugated **estrogens**, administered vaginally 3 nights per week for 6 months. We examined the following outcomes: symptoms, vaginal cellular (cytologic) maturity, endometrial histology, sonographic evaluation of endometrial thickness, Doppler measures of uterine artery blood flow, and serum levels of estrone and **estradiol**. Pre- and post-treatment data were compared for each subject. RESULTS: Satisfactory relief of symptoms occurred in 19 of 20 cases. Vaginal cellular maturation improved significantly with therapy ($P < .01$). There were no significant changes in endometrial thickness, uterine artery blood flow, or serum **estrogen** levels. Endometrial proliferation was observed in one case. CONCLUSIONS: Relief from **atrophic vaginitis** can be achieved with 0.3 mg of conjugated **estrogens** administered vaginally three times per week. Endometrial proliferation may occur at this low dose, albeit rarely.

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=> d 6-10 ibib abs kwic

YOU HAVE REQUESTED DATA FROM FILE 'MEDLINE, CAPLUS, BIOSIS' - CONTINUE? (Y)/N:y

L5 ANSWER 6 OF 46 MEDLINE
ACCESSION NUMBER: 2001154514 MEDLINE
DOCUMENT NUMBER: 21072900 PubMed ID: 11201532
TITLE: **Atrophic vaginitis. Estrogen** can help.
AUTHOR: Anonymous
SOURCE: MAYO CLINIC HEALTH LETTER, (2001 Jan) 19 (1) 6.
Journal code: 8507508. ISSN: 0741-6245.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Consumer Health
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010322
TI **Atrophic vaginitis. Estrogen** can help.

L5 ANSWER 7 OF 46 MEDLINE
ACCESSION NUMBER: 2000296368 MEDLINE
DOCUMENT NUMBER: 20296368 PubMed ID: 10839558
TITLE: Diagnosis and treatment of atrophic vaginitis.
AUTHOR: Bachmann G A; Nevadunsky N S
CORPORATE SOURCE: Division of General Obstetrics and Gynecology, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick 08901, USA.
SOURCE: AMERICAN FAMILY PHYSICIAN, (2000 May 15) 61 (10) 3090-6.
Journal code: 1272646. ISSN: 0002-838X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000622
Last Updated on STN: 20000622
Entered Medline: 20000613
AB Up to 40 percent of postmenopausal women have symptoms of **atrophic vaginitis**. Because the condition is attributable to **estrogen** deficiency, it may occur in premenopausal women who take antiestrogenic medications or who have medical or surgical conditions that result in decreased levels of **estrogen**. The thinned endometrium and increased vaginal pH level induced by **estrogen** deficiency predispose the vagina and urinary tract to infection and mechanical weakness. The earliest symptoms are decreased vaginal lubrication, followed by other vaginal and urinary symptoms that may be exacerbated by superimposed infection. Once other causes of symptoms have been eliminated, treatment usually depends on **estrogen** replacement. **Estrogen** replacement therapy may be provided systemically or locally, but the dosage and delivery method must be individualized. Vaginal moisturizers and lubricants, and participation in coitus may also be beneficial in the treatment of women with **atrophic vaginitis**.
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L5 ANSWER 8 OF 46 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2000208634 MEDLINE
DOCUMENT NUMBER: 20208634 PubMed ID: 10746845
TITLE: Comparison of usefulness of estradiol vaginal tablets and estriol vagitories for treatment of vaginal atrophy.
AUTHOR: Dugal R; Hesla K; Sordal T; Aase K H; Lilleeidet O; Wickstrom E
CORPORATE SOURCE: Soebergtorget Legesenter, Sandefjord, Norway.
SOURCE: ACTA OBSTETRICIA ET GYNECOLOGICA SCANDINAVICA, (2000 Apr) 79 (4) 293-7.
Journal code: 0370343. ISSN: 0001-6349.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000427
Last Updated on STN: 20000427
Entered Medline: 20000414

AB BACKGROUND: **Atrophic vaginitis** is a common condition. This study compared the usefulness of **estradiol** vaginal tablets (EVT) and estriol vagitories (EV) in treatment of **atrophic vaginitis**. METHODS: Ninety-six postmenopausal women with symptoms of **atrophic vaginitis** were treated for 24 weeks with either EVT or with EV. Patients used the medication daily for the first 2 weeks of the study, and twice-weekly thereafter. RESULTS: Both EVT and EV were effective in treating vaginal atrophy and patients in both treatment groups experienced a significant improvement in vaginal symptoms such as itching, irritation, dryness, and dyspareunia. At the end of the study three (6%) EVT treated women reported leakage and none needed to use sanitary towels. Among the EV treated women 31 (65%) reported leakage and 14 (29%) required sanitary protection. Furthermore, 90% in the EVT group perceived the medication as hygienic compared to 79% in the EV group, and 49% in the EVT group indicated that the product was easy to use compared to 28% in the EV group. Endometrial thickness was increased (1.1 mm with EVT and 0.5 mm on EV) in both treatment groups during the first 2 weeks of the study, but returned to baseline levels when the frequency of drug application was reduced to twice-weekly. CONCLUSIONS: **Estradiol** vaginal tablets provides an effective alternative to traditional forms of local **estrogen** therapy.

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traditional forms of local **estrogen** therapy.

L5 ANSWER 9 OF 46 MEDLINE
ACCESSION NUMBER: 2000269097 MEDLINE
DOCUMENT NUMBER: 20269097 PubMed ID: 10810960
TITLE: 17beta-**estradiol** vaginal tablet versus conjugated equine **estrogen** vaginal cream to relieve menopausal **atrophic vaginitis**.
COMMENT: Comment in: Menopause. 2000 May-Jun;7(3):140-2
AUTHOR: Rioux J E; Devlin C; Gelfand M M; Steinberg W M; Hepburn D S
CORPORATE SOURCE: Departement de gynecologie-obstetrique, Centre Hospitalier de l'Universite Laval, Ste-Foy, Quebec, Canada.
SOURCE: MENOPAUSE, (2000 May-Jun) 7 (3) 156-61.
Journal code: 9433353. ISSN: 1072-3714.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000728
Last Updated on STN: 20000728
Entered Medline: 20000714

AB OBJECTIVES: The efficacy and safety of 25-microg 17beta-**estradiol** vaginal tablets (Vagifem) were assessed and compared with 1.25-mg conjugated equine **estrogen** vaginal cream (Premarin Vaginal Cream) for the relief of menopausal-derived **atrophic vaginitis**, resulting from **estrogen** deficiency. DESIGN: In a multicenter, open-label, randomized, parallel-group study, 159 menopausal women were treated for 24 weeks with either vaginal tablets or vaginal cream. Efficacy was evaluated by relief of vaginal symptoms and concentrations of serum **estradiol** and follicle-stimulating hormone. Safety was monitored by the incidence of adverse events, evaluation of endometrial biopsies, and clinical laboratory results. Patients also assessed the acceptability of the study medications. RESULTS: Composite scores of vaginal symptoms (dryness, soreness, and irritation) demonstrated that both treatments provided equivalent relief of the symptoms of **atrophic vaginitis**. At weeks 2, 12, and 24, increases in serum **estradiol** concentrations and suppression of follicle-stimulating hormone were observed in significantly more patients who were using the vaginal cream than in those who were using the vaginal tablets ($p < 0.001$). Fewer patients who were using the vaginal tablets experienced endometrial proliferation or hyperplasia compared with patients who were using the vaginal cream. Significantly more patients who were using the vaginal tablets rated their medication favorably than did patients who were using the vaginal cream ($p < \text{or} = 0.001$). Patients who were receiving the vaginal tablets also had a lower incidence of patient withdrawal (10% versus 32%). CONCLUSIONS: Treatment regimens with 25-microg 17beta-**estradiol** vaginal tablets and with 1.25-mg conjugated equine **estrogen** vaginal cream were equivalent in relieving symptoms of **atrophic vaginitis**. The vaginal tablets demonstrated a localized effect without appreciable systemic **estradiol** increases or estrogenic side effects. Vaginal tablet therapy resulted in greater patient acceptance and lower withdrawal rates compared with vaginal cream therapy.

TI 17beta-**estradiol** vaginal tablet versus conjugated equine **estrogen** vaginal cream to relieve menopausal **atrophic vaginitis**.

AB OBJECTIVES: The efficacy and safety of 25-microg 17beta-**estradiol**

vaginal tablets (Vagifem) were assessed and compared with 1.25-mg conjugated equine **estrogen** vaginal cream (Premarin Vaginal Cream) for the relief of menopausal-derived **atrophic vaginitis**, resulting from **estrogen** deficiency. DESIGN: In a multicenter, open-label, randomized, parallel-group study, 159 menopausal women were treated for 24 weeks with either vaginal tablets or vaginal cream. Efficacy was evaluated by relief of vaginal symptoms and concentrations of serum **estradiol** and follicle-stimulating hormone. Safety was monitored by the incidence of adverse events, evaluation of endometrial biopsies, and clinical laboratory results.. . . Composite scores of vaginal symptoms (dryness, soreness, and irritation) demonstrated that both treatments provided equivalent relief of the symptoms of **atrophic vaginitis**. At weeks 2, 12, and 24, increases in serum **estradiol** concentrations and suppression of follicle-stimulating hormone were observed in significantly more patients who were using the vaginal cream than in. . . receiving the vaginal tablets also had a lower incidence of patient withdrawal (10% versus 32%). CONCLUSIONS: Treatment regimens with 25-microg 17beta-**estradiol** vaginal tablets and with 1.25-mg conjugated equine **estrogen** vaginal cream were equivalent in relieving symptoms of **atrophic vaginitis**. The vaginal tablets demonstrated a localized effect without appreciable systemic **estradiol** increases or estrogenic side effects. Vaginal tablet therapy resulted in greater patient acceptance and lower withdrawal rates compared with vaginal. . .

L5 ANSWER 10 OF 46 MEDLINE
ACCESSION NUMBER: 1999075087 MEDLINE
DOCUMENT NUMBER: 99075087 PubMed ID: 9857760
TITLE: [Pharma-clinics. Drug of the month. Premelle (conjugated estrogens + medroxyprogesterone].
Pharma-clinics. Le médicament du mois. Premelle (oestrogenes conjugues + medroxyprogesterone).
AUTHOR: Scheen A J
CORPORATE SOURCE: Universite de Liege.
SOURCE: REVUE MEDICALE DE LIEGE, (1998 Oct) 53 (10) 638-40.
Journal code: 0404317. ISSN: 0370-629X.
PUB. COUNTRY: Belgium
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990202
Last Updated on STN: 19990202
Entered Medline: 19990119

AB Premelle, commercialised by Wyeth-Lederle, is a combination of conjugated **estrogens** 0.625 mg and medroxyprogesterone acetate 5 mg which is indicated in the treatment of menopause-associated problems, among which vasomotor symptoms, **atrophic vaginitis** and/or urethritis, and in the prevention and treatment of post-menopausal osteoporosis. It is presented in two formulations, Premelle cyclic 5 and Premelle 5. The former, in which the progestagen is only given during the last 14 out of 28 days of the treatment cycle, is accompanied by regular bleeding and thus preferably indicated during perimenopause whereas the latter, in which the progestagen is given continuously and results in amenorrhea, is mostly indicated after menopause in order to improve long-term compliance.

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osteoporosis. It is presented in two formulations, Premelle cyclic 5. .

=> loh y
LOH IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	1.38	31.96

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-1.24

STN INTERNATIONAL LOGOFF AT 16:24:28 ON 07 OCT 2002

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PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Apr 08	"Ask CAS" for self-help around the clock
NEWS 3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 4	Apr 09	ZDB will be removed from STN
NEWS 5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 9	Jun 03	New e-mail delivery for search results now available
NEWS 10	Jun 10	MEDLINE Reload
NEWS 11	Jun 10	PCTFULL has been reloaded
NEWS 12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS 13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS 14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS 15	Jul 30	NETFIRST to be removed from STN
NEWS 16	Aug 08	CANCERLIT reload
NEWS 17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18	Aug 08	NTIS has been reloaded and enhanced
NEWS 19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS 22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 23	Sep 03	JAPIO has been reloaded and enhanced
NEWS 24	Sep 16	Experimental properties added to the REGISTRY file
NEWS 25	Sep 16	Indexing added to some pre-1967 records in CA/CAPLUS
NEWS 26	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 27	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985

NEWS EXPRESS	February 1 CURRENT WINDOWS VERSION IS V6.0d, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

* * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

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FILE 'HOME' ENTERED AT 15:51:23 ON 07 OCT 2002

=> il medl caplu biosis
IL IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> fil medl caplu biosis
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'MEDLINE' ENTERED AT 15:51:38 ON 07 OCT 2002

FILE 'CAPLUS' ENTERED AT 15:51:38 ON 07 OCT 2002
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FILE 'BIOSIS' ENTERED AT 15:51:38 ON 07 OCT 2002
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=> s atrophic vaginitis
L1          124 ATROPHIC VAGINITIS

=> s estrogen or estradiol
L2       351401 ESTROGEN OR ESTRADIOL

=> s l1 and l2
L3           86 L1 AND L2

=> s l1 (S) l2
L4           59 L1 (S) L2

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5            46 DUP REM L4 (13 DUPLICATES REMOVED)

=> d 41-46 ibib abs kwic

L5   ANSWER 41 OF 46     MEDLINE
ACCESSION NUMBER:    77168123     MEDLINE
DOCUMENT NUMBER:     77168123   PubMed ID: 870690
TITLE:               Exogenous estrogens and endometrial carcinoma: review and
                     comments for the clinician.
AUTHOR:              Berger G S; Fowler W C Jr
SOURCE:              JOURNAL OF REPRODUCTIVE MEDICINE, (1977 Apr) 18 (4) 177-80.
                     Journal code: 0173343. ISSN: 0024-7758.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         197706
ENTRY DATE:          Entered STN: 19900313
                     Last Updated on STN: 19900313
                     Entered Medline: 19770630
AB   It is justifiable to have reservations about the significance of the data
     available at this time on a possible increase in the risk of a patient's
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developing endometrial cancer if **estrogen** replacement therapy has been prescribed for her. Hopefully, additional studies currently being conducted will help to clarify the issue further. In the meantime, clinicians need guidelines on the use of **estrogen** replacement therapy. **Estrogen** is indicated in the premenopausal woman who has had surgical or radiation castration for treatment of disease. Menopausal women with severe vasomotor instability or **atrophic vaginitis** should also be considered for **estrogen** replacement therapy. In the latter situation, topical administration may be adequate. Contraindications to **estrogen** replacement include undiagnosed vaginal bleeding, breast cancer history of thromboembolic disease, liver disease, uterine leiomyomata, hypertension, diabetes, migraine headaches or gall bladder disease. In patients for whom **estrogens** are contraindicated, **atrophic vaginitis** can be treated with local **estrogens** and vasomotor symptoms with sedatives such as phenobarbital and belladonna. Before **estrogen** treatment is begun, a medical history and physical examination that look for possible contraindications are required. Obviously, any woman with abnormal uterine bleeding in the menopausal age group requires a procedure that provides tissue for histopathologic examination. Although postmenopausal women taking **estrogen** may have uterine bleeding related to the hormone, such bleeding cannot be assumed to be due to the therapy and always requires evaluation. The lowest dose effective in controlling a patient's symptoms should be administered, preferably in cyclic fashion. Whether the addition of a progestational compound at cyclic intervals has a beneficial effect on the endometrium is a matter of conjecture at this time. Requirement for continuing therapy should be reevaluated at least on an annual basis and preferably more often. In conclusion, a quote from Graber and Barber is appropriate: "The entire picture of routine postmenopausal **estrogen** therapy is in a state of complete confusion. We must proceed with circumspection and caution. We need less passion, fewer hypotheses, and more facts."

AB . . . the data available at this time on a possible increase in the risk of a patient's developing endometrial cancer if **estrogen** replacement therapy has been prescribed for her. Hopefully, additional studies currently being conducted will help to clarify the issue further. In the meantime, clinicians need guidelines on the use of **estrogen** replacement therapy. **Estrogen** is indicated in the premenopausal woman who has had surgical or radiation castration for treatment of disease. Menopausal women with severe vasomotor instability or **atrophic vaginitis** should also be considered for **estrogen** replacement therapy. In the latter situation, topical administration may be adequate. Contraindications to **estrogen** replacement include undiagnosed vaginal bleeding, breast cancer history of thromboembolic disease, liver disease, uterine leiomyomata, hypertension, diabetes, migraine headaches or gall bladder disease. In patients for whom **estrogens** are contraindicated, **atrophic vaginitis** can be treated with local **estrogens** and vasomotor symptoms with sedatives such as phenobarbital and belladonna. Before **estrogen** treatment is begun, a medical history and physical examination that look for possible contraindications are required. Obviously, any woman with. . . uterine bleeding in the menopausal age group requires a procedure that provides tissue for histopathologic examination. Although postmenopausal women taking **estrogen** may have uterine bleeding related to the hormone, such bleeding cannot be assumed to be due to the therapy and. . . and preferably more often. In conclusion, a quote from Graber and Barber is appropriate: "The entire picture of routine postmenopausal **estrogen** therapy is in a state of complete confusion. We must proceed with circumspection and caution. We need less passion, fewer. .